

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

TAKEDA PHARMACEUTICAL
COMPANY LTD., TAKEDA
PHARMACEUTICALS U.S.A., INC.,
TAKEDA PHARMACEUTICALS
AMERICA, INC., and TAKEDA
IRELAND LIMITED,

Plaintiffs,

v.

TORRENT PHARMACEUTICALS LTD.
and TORRENT PHARMA INC.,

Defendants.

TAKEDA PHARMACEUTICAL
COMPANY LTD., TAKEDA
PHARMACEUTICALS U.S.A., INC.,
TAKEDA PHARMACEUTICALS
AMERICA, INC., and TAKEDA
IRELAND LIMITED,

Plaintiffs,

v.

INDOCO REMEDIES LTD.,

Defendant.

Civil Action No. 17-3186 (SRC)(CLW)
(CONSOLIDATED)
(Filed Electronically)

Civil Action No. 17-7301 (SRC)(CLW)
(Filed Electronically)

**DECLARATION OF CHRISTOPHER J. HARNETT, ESQ. IN SUPPORT OF
PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT**

I, Christopher J. Harnett, state and declare as follows:

I am an attorney at the law firm of Jones Day, and counsel for Plaintiffs' and Counterclaim-Defendants Takeda Pharmaceutical Co. Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Ltd. (collectively, "Takeda") in the above-captioned matter. I am admitted to practice before the Court in the above-captioned matter. I submit this declaration in support of Takeda's Memorandum of Law in Support of its Motion for Summary Judgment of Infringement and Validity.

(1) Attached hereto as **Exhibit 1** is a true and correct copy of U.S. Patent No. 7,807,689 (the '689 patent), entitled "Dipeptidyl Peptidase Inhibitors," issued by the United States Patent and Trademark Office ("USPTO") on October 5, 2010;

(2) Attached hereto as **Exhibit 2** is a true and correct copy of the Orange Book Listing for NESINA®, available at
https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=022271&Appl_type=N;

(3) Attached hereto as **Exhibit 3** is a true and correct copy of the Orange Book Listing for KAZANO®, available at
https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=203414&Appl_type=N;

(4) Attached hereto as **Exhibit 4** is a true and correct copy of the Orange Book Listing for OSENI®, available at
https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=004&Appl_No=022426&Appl_type=N;

- (5) Attached hereto as **Exhibit 5** is a true and correct copy of NESINA®'s Product Label;
- (6) Attached hereto as **Exhibit 6** is a true and correct copy of KAZANO®'s Product Label;
- (7) Attached hereto as **Exhibit 7** is a true and correct copy of OSENI®'s Product Label;
- (8) Attached hereto as **Exhibit 8** is a true and correct copy of the NESINA® NDA Approval Letter (NDA No. 022271) from FDA, dated January 25, 2013;
- (9) Attached hereto as **Exhibit 9** is a true and correct copy of the KAZANO® NDA Approval Letter (NDA No. 203414) from FDA, dated January 25, 2013;
- (10) Attached hereto as **Exhibit 10** is a true and correct copy of the OSENI® NDA Approval Letter (NDA No. 022426) from FDA, dated January 25, 2013;
- (11) Attached hereto as **Exhibit 11** is a true and correct copy of the Opening Expert Report of Dana Ferraris, Ph.D. Regarding the Invalidity of U.S. Patent Nos. 7,807,689, 8,288,539; and 8,173,663 filed June 14, 2019;
- (12) Attached hereto as **Exhibit 12** is a true and correct copy of the Reply Report of Dana Ferraris, Ph.D. Regarding the Invalidity of U.S. Patent Nos. 7,807,689, 8,288,539; and 8,173,663 filed August 23, 2019;
- (13) Attached hereto as **Exhibit 13** is a true and correct copy of the Opening Expert Report of David P. Rotella, Ph.D. Regarding the Invalidity of U.S. Patent No. 7,807,689 filed June 14, 2019;

(14) Attached hereto as **Exhibit 14** is a true and correct copy of the Reply Expert Report of David P. Rotella, Ph.D. Regarding the Invalidity of U.S. Patent No. 7,807,689 filed August 23, 2019;

(15) Attached hereto as **Exhibit 15** is a true and correct copy of Canadian Patent CA 2,435,730;

(16) Attached hereto as **Exhibit 16** is a true and correct copy of the WO 2003/004496 publication (international publication date Jan. 16, 2003);

(17) Attached hereto as **Exhibit 17** is a true and correct copy of Wiedeman, P., et al., "Dipeptidyl Peptidase IV Inhibitors For The Treatment Of Impaired Glucose Tolerance And Type 2 Diabetes," 4(4) Current Op. Investigational Drugs 412-420 (Apr. 2003);

(18) Attached hereto as **Exhibit 18** is a true and correct copy of Böhm et al., "Scaffold hopping," Drug Discovery Today: Technologies 2004, Vol. 1, No. 3, 217-223;

(19) Attached hereto as **Exhibit 19** is a true and correct copy of "Asetex, Structural Genomix, and Syrrx," 10 Chemistry & Biology, 95-98 (February 2003);

(20) Attached hereto as **Exhibit 20** is a true and correct copy of Aertgeerts, K., et al., "Crystal Structure Of Human Dipeptidyl Peptidase IV In Complex With A Decapeptide Reveals Details On Substrate Specificity And Tetrahedral Intermediate Formulation", 13(2) Protein Sci. 412-421 (Feb. 2004);

(21) Attached hereto as **Exhibit 21** is a true and correct copy of Engel, M., et al., "The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism", 100(9) PNAS 5063-068 (Apr. 29, 2003);

(22) Attached hereto as **Exhibit 22** is a true and correct copy of Evans, D., "Dipeptidyl peptidase IV inhibitors", 5(6) IDrugs 577-585 (June 2002);

(23) Attached hereto as **Exhibit 23** is a true and correct copy of Lambeir, A., "Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV", 40(3) Crit. Rev. Clin. Lab. Sci. 209-294, 216 (Jun. 2003);

(24) Attached hereto as **Exhibit 24** is a true and correct copy of excerpts from Richard B. Silverman, "The Organic Chemistry of Drug Design and Drug Action," 7-120 (2d ed. 2004);

(25) Attached hereto as **Exhibit 25** is a true and correct copy of Zhang, Zhiyuan et al., "Design and Synthesis of Pyrimidinone and Pyrimidinedione Inhibitors of Dipeptidyl Peptidase IV", 54 J. Med. Chem. 510-524 (2011);

(26) Attached hereto as **Exhibit 26** is a true and correct copy of U.S. Patent No. 5,142,051, "N Phosphonylmethoxyalkyl Derivatives of Pyrimidine and Purine Bases and a Therapeutical Composition Therefrom with Antiviral Activity", issued Aug. 25, 1992;

(27) Attached hereto as **Exhibit 27** is a true and correct copy of U.S. Patent No. 5,780,476, "Hydroxyl-Containing Xanthine Compounds", issued July 14, 1998;

(28) Attached hereto as **Exhibit 28** is a true and correct copy of Davies, T.G., et al., "Structure-based design of cyclin-dependent kinase inhibitors", 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002);

(29) Attached hereto as **Exhibit 29** is a true and correct copy of Villhauer, Edward B., Chapter 19. DPP-IV Inhibition and Therapeutic Potential, ANNUAL REPORTS IN MEDICINAL CHEMISTRY 191, 194 (2001);

(30) Attached hereto as **Exhibit 30** is a true and correct copy of Berge, Stephen M., et al., Pharmaceutical Salts, 66 J. Pharm. Sci., 1, 1-19, (1977);

(31) Attached hereto as **Exhibit 31** is a true and correct copy of L.D. Bighley, S.M. Berge, & D.C. Monkhouse, Salt Forms of Drugs and Absorption, Encyclopedia Pharm. Tech. 453 (1996);

(32) Attached hereto as **Exhibit 32** is a true and correct copy of excerpts from Stahl, et al., Eds., Handbook of Pharmaceutical Salts 273 (2002);

(33) Attached hereto as **Exhibit 33** is a true and correct copy of U.S. Patent No. 7,723,344 entitled “Dipeptidyl Peptidase Inhibitors,” issued by the United States Patent and Trademark Office (“USPTO”) on May 25, 2010;

(34) Attached hereto as **Exhibit 34** is a true and correct copy of Kim et al., “Anti-diabetic Activity of Constituents of Lycii Fructus,” The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998);

(35) Attached hereto as **Exhibit 35** is a true and correct copy of Welch, et al., “Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics”, Vol. 95, pp. 14020-14024 (1998); and

(36) Attached hereto as **Exhibit 36** is a true and correct copy of excerpts from Univ. of Cal School of Pharmacy, “Peptide and Protein Drug Delivery, Chapter 2.: Synthesis of Peptides and Proteins by Chemical and Biotechnological Means”, 95-103 (Vincent H. L. Lee, et al. 1990).

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge.

Executed on: September 10, 2019
New York, New York

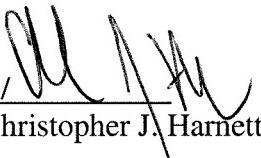
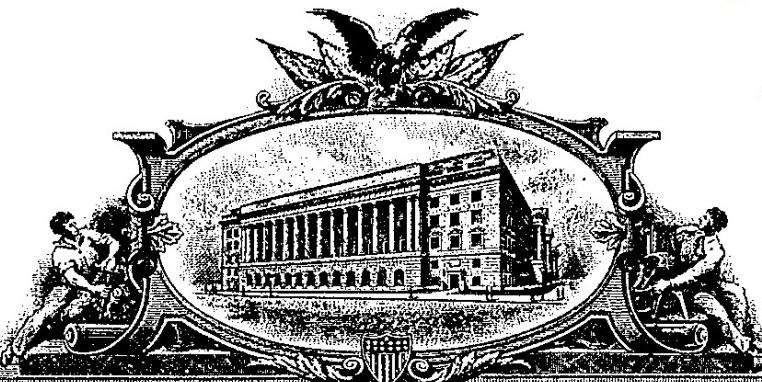

/s/
Christopher J. Harnett

EXHIBIT 1



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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

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United States Patent and Trademark Office

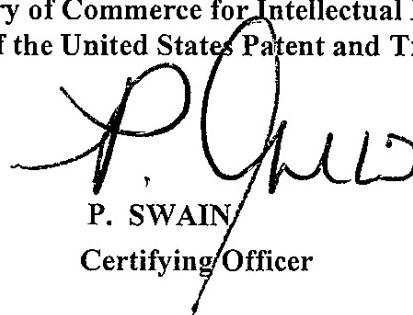
July 14, 2017

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: 7,807,689

ISSUE DATE: *October 05, 2010*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office


P. SWAIN
Certifying Officer





US007807689B2

(12) **United States Patent**
Zhang et al.

(10) Patent No.: **US 7,807,689 B2**
(45) Date of Patent: **Oct. 5, 2010**

(54) **DIPEPTIDYL PEPTIDASE INHIBITORS**

(75) Inventors: **Zhiyuan Zhang, San Diego, CA (US);
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(73) Assignee: **Takeda Pharmaceutical Company
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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 1200 days.

(21) Appl. No.: **11/080,992**

(22) Filed: **Mar. 15, 2005**

(65) **Prior Publication Data**

US 2005/0261271 A1 Nov. 24, 2005

Related U.S. Application Data

(60) Provisional application No. 60/553,571, filed on Mar.
15, 2004, provisional application No. 60/629,524,
filed on Nov. 18, 2004.

(51) **Int. Cl.**

C07D 401/04 (2006.01)
A61K 31/506 (2006.01)
A61P 3/10 (2006.01)
A61P 35/00 (2006.01)

(52) U.S. Cl. **514/274; 544/309**

(58) Field of Classification Search **544/309;
514/274**

See application file for complete search history.

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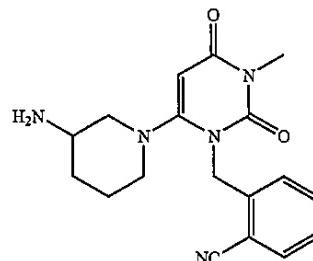
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(Continued)

Primary Examiner—Venkataraman Balasubramanian
(74) Attorney, Agent, or Firm—Mitchell R. Brustein; David J. Weitz

(57) **ABSTRACT**

The present invention provides a compound of the formula:



or stereoisomers or pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof, articles of manufacture comprising the same, and methods of using the same.

51 Claims, 1 Drawing Sheet

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U.S. Patent

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FIGURE 1



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1**DIPEPTIDYL PEPTIDASE INHIBITORS****RELATED APPLICATION**

This application claims the benefit of U.S. Provisional Application No. 60/553,571 filed Mar. 15, 2004 and U.S. Provisional Application No. 60/629,524 filed Nov. 18, 2004, each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to compounds that may be used to inhibit dipeptidyl peptidases as well as compositions of matter and kits comprising these compounds. The present invention also relates to methods for inhibiting dipeptidyl peptidases as well as treatment methods using compounds according to the present invention.

DESCRIPTION OF RELATED ART

Dipeptidyl Peptidase IV (IUBMB Enzyme Nomenclature EC.3.4.14.5) is a type II membrane protein that has been referred to in the literature by a wide variety of names including DPP4, DP4, DAP-IV, FAP β , adenosine deaminase complexing protein 2, adenosine deaminase binding protein (ADA β p), dipeptidyl aminopeptidase IV; Xaa-Pro-dipeptidyl-aminopeptidase; Gly-Pro naphthylamidase; postproline dipeptidyl aminopeptidase IV; lymphocyte antigen CD26; glycoprotein GP110; dipeptidyl peptidase IV; glycylproline aminopeptidase; glycylproline aminopeptidase; X-prolyl dipeptidyl aminopeptidase; pep X; leukocyte antigen CD26; glycylprolyl dipeptidylaniinopeptidase; dipeptidyl-peptide hydrolase; glycylprolyl aminopeptidase; dipeptidyl-aminopeptidase IV; DPP IV/CD26; amino acyl-prolyl dipeptidyl aminopeptidase; T cell triggering molecule Tp103; X-PDAP. Dipeptidyl Peptidase IV is referred to herein as "DPP-IV."

DPP-IV is a non-classical serine aminopeptidase that removes Xaa-Pro dipeptides from the amino terminus (N-terminus) of polypeptides and proteins. DPP-IV dependent slow release of dipeptides of the type X-Gly or X-Ser has also been reported for some naturally occurring peptides.

DPP-IV is constitutively expressed on epithelial and endothelial cells of a variety of different tissues (intestine, liver, lung, kidney and placenta), and is also found in body fluids. DPP-IV is also expressed on circulating T-lymphocytes and has been shown to be synonymous with the cell-surface antigen, CD-26. DPP-IV has been implicated in a number of disease states, some of which are discussed below.

DPP-IV is responsible for the metabolic cleavage of certain endogenous peptides (GLP-1 (7-36), glucagon) in vivo and has demonstrated proteolytic activity against a variety of other peptides (GHRH, NPY, GLP-2, VIP) in vitro.

GLP-1 (7-36) is a 29 amino-acid peptide derived by post-translational processing of proglucagon in the small intestine. GLP-1 (7-36) has multiple actions in vivo including the stimulation of insulin secretion, inhibition of glucagon secretion, the promotion of satiety, and the slowing of gastric emptying. Based on its physiological profile, the actions of GLP-1 (7-36) are believed to be beneficial in the prevention and treatment of type II diabetes and potentially obesity. For example, exogenous administration of GLP-1 (7-36) (continuous infusion) in diabetic patients has been found to be efficacious in this patient population. Unfortunately, GLP-1 (7-36) is degraded rapidly in vivo and has been shown to have a short half-life in vivo ($t_{1/2}=1.5$ minutes).

Based on a study of genetically bred DPP-IV knock out mice and on in vivo/in vitro studies with selective DPP-IV

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inhibitors, DPP-IV has been shown to be the primary degrading enzyme of GLP-1 (7-36) in vivo. GLP-1 (7-36) is degraded by DPP-IV efficiently to GLP-1 (9-36), which has been speculated to act as a physiological antagonist to GLP-1 (7-36). Inhibiting DPP-IV in vivo is therefore believed to be useful for potentiating endogenous levels of GLP-1 (7-36) and attenuating the formation of its antagonist GLP-1 (9-36). Thus, DPP-IV inhibitors are believed to be useful agents for the prevention, delay of progression, and/or treatment of conditions mediated by DPP-IV, in particular diabetes and more particularly, type 2 diabetes mellitus, diabetic dislipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation and obesity.

DPP-IV expression is increased in T-cells upon mitogenic or antigenic stimulation (Mattem, T., et al., *Scand. J. Immunol.*, 1991, 33, 737). It has been reported that inhibitors of DPP-IV and antibodies to DPP-IV suppress the proliferation of mitogen-stimulated and antigen-stimulated T-cells in a dose-dependant manner (Schon, E., et al., *Biol. Chem.*, 1991, 372, 305). Various other functions of T-lymphocytes such as cytokine production, IL-2 mediated cell proliferation and B-cell helper activity have been shown to be dependent on DPP-IV activity (Schon, E., et al., *Scand. J. Immunol.*, 1989, 29, 127). DPP-IV inhibitors, based on boroProline, (Flentke, G. R., et al., *Proc. Nat. Acad. Sci. USA*, 1991, 88, 1556) although unstable, were effective at inhibiting antigen-induced lymphocyte proliferation and IL-2 production in murine CD4+ T-helper cells. Such boronic acid inhibitors have been shown to have an effect in vivo in mice causing suppression of antibody production induced by immune challenge (Kubota, T. et al., *Clin. Exp. Immunol.*, 1992, 89, 192). The role of DPP-IV in regulating T lymphocyte activation may also be attributed, in part, to its cell-surface association with the transmembrane phosphatase, CD45. DPP-IV inhibitors or non-active site ligands may possibly disrupt the CD45-DPP-IV association. CD45 is known to be an integral component of the T-cell signaling apparatus. It has been reported that DPP-IV is essential for the penetration and infectivity of HIV-1 and HIV-2 viruses in CD4+ T-cells (Wakselman, M., Nguyen, C., Mazaleyrat, J.-P., Callebaut, C., Krust, B., Hovassian, A. G., Inhibition of HIV-1 infection of CD 26+ but not CD 26-cells by a potent cyclopeptidic inhibitor of the DPP-IV activity of CD 26. Abstract P.44 of the 24.sup.th European Peptide Symposium 1996). Additionally, DPP-IV has been shown to associate with the enzyme adenosine deaminase (ADA) on the surface of T-cells (Kameoka, J., et al., *Science*, 1993, 26, 466). ADA deficiency causes severe combined immunodeficiency disease (SCID) in humans. This ADA-CD26 interaction may provide clues to the pathophysiology of SCID. It follows that inhibitors of DPP-IV may be useful immunosuppressants (or cytokine release suppressant drugs) for the treatment of among other things: organ transplant rejection; autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis; and the treatment of AIDS.

It has been shown that lung endothelial cell DPP-IV is an adhesion molecule for lung-metastatic rat breast and prostate carcinoma cells (Johnson, R. C., et al., *J. Cell. Biol.*, 1993, 121, 1423). DPP-IV is known to bind to fibronectin and some metastatic tumor cells are known to carry large amounts of fibronectin on their surface. Potent DPP-IV inhibitors may be useful as drugs to prevent metastases of, for example, breast and prostate tumors to the lungs.

High levels of DPP-IV expression have also been found in human skin fibroblast cells from patients with psoriasis, rheumatoid arthritis (RA) and lichen planus (Raynaud, F., et al., *J.*

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Cell. Physiol., 1992, 151, 378). Therefore, DPP-IV inhibitors may be useful as agents to treat dermatological diseases such as psoriasis and lichen planus.

High DPP-IV activity has been found in tissue homogenates from patients with benign prostate hypertrophy and in prostatosomes. These are prostate derived organelles important for the enhancement of sperm forward motility (Vanhoof, G., et al., *Eur. J. Clin. Chem. Clin. Biochem.*, 1992, 30, 333). DPP-IV inhibitors may also act to suppress sperm motility and therefore act as a male contraceptive agent. Conversely, DPP-IV inhibitors have been implicated as novel for treatment of infertility, and particularly human female infertility due to Polycystic ovary syndrome (PCOS, Stein-Leventhal syndrome) which is a condition characterized by thickening of the ovarian capsule and formation of multiple follicular cysts. It results in infertility and amenorrhea.

DPP-IV is thought to play a role in the cleavage of various cytokines (stimulating hematopoietic cells), growth factors and neuropeptides.

Stimulated hematopoietic cells are useful for the treatment of disorders that are characterized by a reduced number of hematopoietic cells or their precursors *in vivo*. Such conditions occur frequently in patients who are immunosuppressed, for example, as a consequence of chemotherapy and/or radiation therapy for cancer. It was discovered that inhibitors of dipeptidyl peptidase type IV are useful for stimulating the growth and differentiation of hematopoietic cells in the absence of exogenously added cytokines or other growth factors or stromal cells. This discovery contradicts the dogma in the field of hematopoietic cell stimulation, which provides that the addition of cytokines or cells that produce cytokines (stromal cells) is an essential element for maintaining and stimulating the growth and differentiation of hematopoietic cells in culture. (See, e.g., PCT Intl. Application No. PCT/US93/017173 published as WO 94/03055).

DPP-IV in human plasma has been shown to cleave N-terminal Tyr-Ala from growth hormone-releasing factor and cause inactivation of this hormone. Therefore, inhibitors of DPP-IV may be useful in the treatment of short stature due to growth hormone deficiency (Dwarfism) and for promoting GH-dependent tissue growth or re-growth.

DPP-IV can also cleave neuropeptides and has been shown to modulate the activity of neuroactive peptides substance P, neuropeptide Y and CLIP (Mentlein, R., Dahms, P., Grandt, D., Kruger, R., Proteolytic processing of neuropeptide Y and peptide YY by dipeptidyl peptidase IV, *Regul. Pept.*, 49, 133, 1993; Wetzel, W., Wagner, T., Vogel, D., Demuth, H.-U., Balschun, D., Effects of the CLIP fragment ACTH 20-24 on the duration of REM sleep episodes, *Neuropeptides*, 31, 41, 1997). Thus DPP-IV inhibitors may also be useful agents for the regulation or normalization of neurological disorders.

Several compounds have been shown to inhibit DPP-IV. Nonetheless, a need still exists for new DPP-IV inhibitors that have advantageous potency, stability, selectivity, toxicity and/or pharmacodynamics properties. In this regard, a novel class of DPP-IV inhibitors are provided herein.

SUMMARY OF THE INVENTION

The present invention relates to compounds that have activity for inhibiting DPP-IV. It is noted that these compounds may also have activity for inhibiting other S9 proteases and thus may be used against these other S9 proteases as well as DPP-IV. The present invention also provides compositions, articles of manufacture and kits comprising these compounds.

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In one embodiment, a pharmaceutical composition is provided that comprises a DPP-IV inhibitor according to the present invention as an active ingredient. Pharmaceutical compositions according to the invention may optionally comprise 0.001%-100% of one or more DPP-IV inhibitors of this invention. These pharmaceutical compositions may be administered or coadministered by a wide variety of routes, including for example, orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, or intrathecally. The compositions may also be administered or coadministered in slow release dosage forms.

The invention is also directed to kits and other articles of manufacture for treating disease states associated with DPP-IV.

In one embodiment, a kit is provided that comprises a composition comprising at least one DPP-IV inhibitor of the present invention in combination with instructions. The instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one DPP-IV inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

Also provided are methods for preparing compounds, compositions and kits according to the present invention. For example, several synthetic schemes are provided herein for synthesizing compounds according to the present invention.

Also provided are methods for using compounds, compositions, kits and articles of manufacture according to the present invention.

In one embodiment, the compounds, compositions, kits and articles of manufacture are used to inhibit DPP-IV.

In another embodiment, the compounds, compositions, kits and articles of manufacture are used to treat a disease state for which DPP-IV possesses activity that contributes to the pathology and/or symptomology of the disease state.

In another embodiment, a compound is administered to a subject wherein DPP-IV activity within the subject is altered, preferably reduced.

In another embodiment, a prodrug of a compound is administered to a subject that is converted to the compound *in vivo* where it inhibits DPP-IV.

In another embodiment, a method of inhibiting DPP-IV is provided that comprises contacting DPP-IV with a compound according to the present invention.

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In another embodiment, a method of inhibiting DPP-IV is provided that comprises causing a compound according to the present invention to be present in a subject in order to inhibit DPP-IV in vivo.

In another embodiment, a method of inhibiting DPP-IV is provided that comprises administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits DPP-IV in vivo. It is noted that the compounds of the present invention may be the first or second compounds.

In another embodiment, a therapeutic method is provided that comprises administering a compound according to the present invention.

In another embodiment, a method of inhibiting cell proliferation is provided that comprises contacting a cell with an effective amount of a compound according to the present invention.

In another embodiment, a method of inhibiting cell proliferation in a patient is provided that comprises administering to the patient a therapeutically effective amount of a compound according to the present invention.

In another embodiment, a method of treating a condition in a patient which is known to be mediated by DPP-IV, or which is known to be treated by DPP-IV inhibitors, comprising administering to the patient a therapeutically effective amount of a compound according to the present invention.

In another embodiment, a method is provided for using a compound according to the present invention in order to manufacture a medicament for use in the treatment of disease state which is known to be mediated by DPP-IV, or which is known to be treated by DPP-IV inhibitors.

In another embodiment, a method is provided for treating a disease state for which DPP-IV possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: causing a compound according to the present invention to be present in a subject in a therapeutically effective amount for the disease state.

In another embodiment, a method is provided for treating a disease state for which DPP-IV possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a first compound to a subject that is converted in vivo to a second compound such that the second compound is present in the subject in a therapeutically effective amount for the disease state. It is noted that the compounds of the present invention may be the first or second compounds.

In another embodiment, a method is provided for treating a disease state for which DPP-IV possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a compound according to the present invention to a subject such that the compound is present in the subject in a therapeutically effective amount for the disease state.

In another embodiment, a method is provided for treating a cell proliferative disease state comprising treating cells with a compound according to the present invention in combination with an anti-proliferative agent, wherein the cells are treated with the compound according to the present invention before, at the same time, and/or after the cells are treated with the anti-proliferative agent, referred to herein as combination therapy. It is noted that treatment of one agent before another is referred to herein as sequential therapy, even if the agents are also administered together. It is noted that combination therapy is intended to cover when agents are administered before or after each other (sequential therapy) as well as when the agents are administered at the same time.

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Examples of diseases that may be treated by administration of compounds and compositions according to the present invention include, but are not limited to conditions mediated by DPP-IV, in particular diabetes, more particular type 2 diabetes mellitus, diabetic dyslipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation, obesity, immunosuppressants or cytokine release regulation, autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis, AIDS, cancers (prevention of metastases, for example, breast and prostate tumors to the lungs), dermatological diseases such as psoriasis and lichen planus, treatment of female infertility, osteoporosis, male contraception and neurological disorders.

It is noted in regard to all of the above embodiments that the present invention is intended to encompass all pharmaceutically acceptable ionized forms (e.g., salts) and solvates (e.g., hydrates) of the compounds, regardless of whether such ionized forms and solvates are specified since it is well known in the art to administer pharmaceutical agents in an ionized or solvated form. It is also noted that unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all possible stereoisomers (e.g., enantiomers or diastereomers depending on the number of chiral centers), independent of whether the compound is present as an individual isomer or a mixture of isomers. Further, unless otherwise specified, recitation of a compound is intended to encompass all possible resonance forms and tautomers. With regard to the claims, the language "compound comprising the formula" is intended to encompass the compound and all pharmaceutically acceptable ionized forms and solvates, all possible stereoisomers, and all possible resonance forms and tautomers unless otherwise specifically specified in the particular claim.

It is further noted that prodrugs may also be administered which are altered in vivo and become a compound according to the present invention. The various methods of using the compounds of the present invention are intended, regardless of whether prodrug delivery is specified, to encompass the administration of a prodrug that is converted in vivo to a compound according to the present invention. It is also noted that certain compounds of the present invention may be altered in vivo prior to inhibiting DPP-IV and thus may themselves be prodrugs for another compound. Such prodrugs of another compound may or may not themselves independently have DPP-IV inhibitory activity.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 illustrates a ribbon diagram overview of the structure of DPP-IV, highlighting the secondary structural elements of the protein.

DEFINITIONS

Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

"Alicyclic" means a moiety comprising a non-aromatic ring structure. Alicyclic moieties may be saturated or partially unsaturated with one, two or more double or triple bonds. Alicyclic moieties may also optionally comprise heteroatoms such as nitrogen, oxygen and sulfur. The nitrogen atoms can be optionally quaternized or oxidized and the sulfur atoms can be optionally oxidized. Examples of alicyclic moieties include, but are not limited to moieties with C3-C8 rings such

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as cyclopropyl, cyclohexane, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptene, cycloheptadiene, cyclooctane, cyclooctene, and cyclooctadiene.

“Aliphatic” means a moiety characterized by a straight or branched chain arrangement of constituent carbon atoms and may be saturated or partially unsaturated with one, two or more double or triple bonds.

“Alkenyl” represented by itself means a straight or branched, unsaturated, aliphatic radical having a chain of carbon atoms having at least one double bond between adjacent carbon atoms. C_x -alkenyl and $C_{x,y}$ -alkenyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{2-6} alkenyl includes alkenyls that have a chain of between 2 and 6 carbons.

“Alkoxy” means an oxygen moiety having a further alkyl substituent. The alkoxy groups of the present invention can be optionally substituted.

“Alkyl” represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having a chain of carbon atoms, optionally with oxygen (See “oxaalkyl”) or nitrogen atoms (See “aminoalkyl”) between the carbon atoms. C_x -alkyl and $C_{x,y}$ -alkyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkyl includes alkyls that have a chain of between 1 and 6 carbons (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl, heteroarylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C_{6-10}) aryl(C_{1-3})alkyl includes, benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-thienylmethyl, 2-pyridinylmethyl and the like).

“Alkylene”, unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical. C_x -alkylene and $C_{x,y}$ -alkylene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkylene includes methylene ($—CH_2—$), ethylene ($—CH_2CH_2—$), trimethylene ($—CH_2CH_2CH_2—$), tetramethylene ($—CH_2CH_2CH_2CH_2—$), 2-butylene ($—CH_2CH=CHCH_2—$), 2-methyltetramethylene ($—CH_2CH(CH_3)CH_2CH_2—$), pentamethylene ($—CH_2CH_2CH_2CH_2CH_2—$) and the like.

“Alkylidene” means a straight or branched saturated or unsaturated, aliphatic radical connected to the parent molecule by a double bond. C_x -alkylidene and $C_{x,y}$ -alkylidene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkylidene includes methylene ($=CH_2$), ethylidene ($=CHCH_3$), isopropylidene ($=C(CH_3)_2$), propylidene ($=CHCH_2CH_3$), allylidene ($=CH—CH=CH_2$), and the like.

“Alkynyl” represented by itself means a straight or branched, unsaturated, aliphatic radical having a chain of carbon atoms having at least one triple bond between adjacent carbon atoms. C_x -alkynyl and $C_{x,y}$ -alkynyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{2-6} alkynyl includes alkynyls that have a chain of between 2 and 6 carbons.

“Amino” means a nitrogen moiety having two further substituents where a hydrogen or carbon atom is attached to the nitrogen. For example, representative amino groups include $—NH_2$, $—NHCH_3$, $—N(CH_3)_2$, $—NHC_{1-3}$ -alkyl, $—N(C_{1-3}$ -alkyl) $_2$ and the like. Unless indicated otherwise, the compounds of the invention containing amino moieties may

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include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, tert-butoxycarbonyl, benzyloxycarbonyl, and the like.

“Aminoalkyl” means an alkyl, as defined above, except where one or more substituted or unsubstituted nitrogen atoms ($—N—$) are positioned between carbon atoms of the alkyl. For example, an (C_{2-6}) aminoalkyl refers to a chain comprising between 2 and 6 carbons and one or more nitrogen atoms positioned between the carbon atoms.

“Animal” includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

“Aromatic” means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi electrons is equal to $4n+2$. An aromatic ring may be such that the ring atoms are only carbon atoms or may include carbon and non-carbon atoms (see Heteroaryl).

“Aryl” means a monocyclic or polycyclic ring assembly wherein each ring is aromatic or when fused with one or more rings forms an aromatic ring assembly. If one or more ring atoms is not carbon (e.g., N, S), the aryl is a heteroaryl. C_x -aryl and $C_{x,y}$ -aryl are typically used where X and Y indicate the number of atoms in the ring.

“Bicycloalkyl” means a saturated or partially unsaturated fused bicyclic or bridged polycyclic ring assembly.

“Bicycloaryl” means a bicyclic ring assembly wherein the rings are linked by a single bond or fused and at least one of the rings comprising the assembly is aromatic. C_x -bicycloaryl and $C_{x,y}$ -bicycloaryl are typically used where X and Y indicate the number of carbon atoms in the bicyclic ring assembly and directly attached to the ring.

“Bridging ring” as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where two ring atoms that are common to both rings are not directly bound to each other. Non-exclusive examples of common compounds having a bridging ring include borneol, norbornane, 7-oxabicyclo[2.2.1]heptane, and the like. One or both rings of the bicyclic system may also comprise heteroatoms.

“Carbamoyl” means the radical $—OC(O)NR_aR_b$ where R_a and R_b are each independently two further substituents where a hydrogen or carbon atom is attached to the nitrogen.

“Carbocycle” means a ring consisting of carbon atoms.

“Carbocyclic ketone derivative” means a carbocyclic derivative wherein the ring contains a $—CO—$ moiety.

“Carbonyl” means the radical $—CO—$. It is noted that the carbonyl radical may be further substituted with a variety of substituents to form different carbonyl groups including acids, acid halides, aldehydes, amides, esters, and ketones.

“Carboxy” means the radical $—CO_2—$. It is noted that compounds of the invention containing carboxy moieties may include protected derivatives thereof, i.e., where the oxygen is substituted with a protecting group. Suitable protecting groups for carboxy moieties include benzyl, tert-butyl, and the like.

“Cyano” means the radical $—CN$.

“Cycloalkyl” means a non-aromatic, saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly. C_x -cycloalkyl and $C_{x,y}$ -cycloalkyl are typically used where X and Y indicate the number of carbon atoms in the ring assembly. For example, C_{3-10} cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamant-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxabicyclo[2.2.1]hept-1-yl, and the like.

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"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic or polycyclic ring assembly. C_X cycloalkylene and C_{X-Y} cycloalkylene are typically used where X and Y indicate the number of carbon atoms in the ring assembly.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Fused ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where the ring atoms that are common to both rings are directly bound to each other. Non-exclusive examples of common fused rings include decalin, naphthalene, anthracene, phenanthrene, indole, furan, benzofuran, quinoline, and the like. Compounds having fused ring systems may be saturated, partially saturated, carbocyclics, heterocyclics, aromatics, heteroaromatics, and the like.

"Halo" means fluoro, chloro, bromo or iodo.

"Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C_{1-3})alkyl includes chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Heteroatom" refers to an atom that is not a carbon atom. Particular examples of heteroatoms include, but are not limited to nitrogen, oxygen, and sulfur.

"Heteroatom moiety" includes a moiety where the atom by which the moiety is attached is not a carbon. Examples of heteroatom moieties include $-N\equiv-$, $-NR_c-$, $-N^+(O^-)=$, $-O-$, $-S-$ or $-S(O)_2-$, wherein R_c is further substituent.

"Heterobicycloalkyl" means bicycloalkyl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example hetero(C_{9-12}) bicycloalkyl as used in this application includes, but is not limited to, 3-aza-bicyclo[4.1.0]hept-3-yl, 2-aza-bicyclo[3.1.0]hex-2-yl, 3-aza-bicyclo[3.1.0]hex-3-yl, and the like.

"Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms is replaced by a heteroatom.

"Heteraryl" means a cyclic aromatic group having five or six ring atoms, wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. The nitrogen atoms can be optionally quaternized and the sulfur atoms can be optionally oxidized. Heteraryl groups of this invention include, but are not limited to, those derived from furan, imidazole, isothiazole, isoxazole, oxadiazole, oxazole, 1,2,3-oxadiazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrolidine, thiazole, 1,3,4-thiadiazole, triazole and tetrazole. "Heteraryl" also includes, but is not limited to, bicyclic or tricyclic rings, wherein the heteroaryl ring is fused to one or two rings independently selected from the group consisting of an aryl ring, a cycloalkyl ring, a cycloalkenyl ring, and another monocyclic heteroaryl or heterocycloalkyl ring. These bicyclic or tricyclic heteroaryls include, but are not limited to, those derived from benzo[b]furan, benzo[b]thiophene, benzimidazole, imidazo[4,5-c]pyridine, quinazoline, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, thieno[2,3-b]pyridine, indolizine, imidazo[1,2-a]pyridine, quinoline, isoquinoline, phthalazine, quinoxaline, naphthyridine, quinolizine, indole, isoindole, indazole, indoline, benzoxazole, benzopyrazole, benzothiazole, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrimidine, imidazo[1,2-c]pyrimidine, imidazo[1,5-a]pyrimidine, imidazo[1,5-c]pyrimidine, pyrrolo[2,3-b]pyridine, pyrrolo[2,3-

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c]pyridine, pyrrolo[3,2-c]pyridine, pyrrolo[3,2-b]pyridine, pyrrolo[2,3-d]pyrimidine, pyrrolo[3,2-d]pyrimidine, pyrrolo[2,3-b]pyrazine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrimidine, pyrrolo[1,2-a]pyrazine, triazo[1,5-a]pyridine, pteridine, purine, carbazole, acridine, phenazine, phenothiazine, phenoxazine, 1,2-dihydropyrrolo[3,2,1-h]indole, indolizine, pyrido[1,2-a]indole and 2 (1H)-pyridinone. The bicyclic or tricyclic heteroaryl rings can be attached to the parent molecule through either the heteroaryl group itself or the aryl, cycloalkyl, cycloalkenyl or heterocycloalkyl group to which it is fused. The heteroaryl groups of this invention can be substituted or unsubstituted.

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example, hetero(C_{4-10})bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, tetrahydroisoquinolinyl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the atoms forming the ring is a heteroatom selected, independently from N, O, or S. Non-exclusive examples of heterocycloalkyl include pipеридил, 4-морфолил, 4-піперазинил, пурілініл, перхідропіролізинил, 1,4-діаза-перхідроепініл, 1,3-діоксаніл, 1,4-діоксаніл и the like.

"Hydroxy" means the radical $-OH$.

"Iminoketone derivative" means a derivative comprising the moiety $\text{---C}(\text{NR})\text{---}$, wherein R comprises a hydrogen or carbon atom attached to the nitrogen.

"Isomers" mean any compound having an identical molecular formulae but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers." A carbon atom bonded to four nonidentical substituents is termed a "chiral center." A compound with one chiral center has two enantiomeric forms of opposite chirality. A mixture of the two enantiomeric forms is termed a "racemic mixture." A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture." When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the R- and S-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992).

"Nitro" means the radical $-NO_2$.

"Oxaalkyl" means an alkyl, as defined above, except where one or more oxygen atoms (---O---) are positioned between carbon atoms of the alkyl. For example, an (C_{2-6})oxaalkyl refers to a chain comprising between 2 and 6 carbons and one or more oxygen atoms positioned between the carbon atoms.

"Oxoalkyl" means an alkyl, further substituted with a carbonyl group. The carbonyl group may be an aldehyde, ketone, ester, amide, acid or acid chloride.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise unde-

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sirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of inhibitors of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanesulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo [2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, 30 tromethamine, N-methylglucamine and the like.

"Prodrug" means a compound that is convertible in vivo metabolically into an inhibitor according to the present invention. The prodrug itself may or may not also have DPP-IV inhibitory activity. For example, an inhibitor comprising a hydroxy group may be administered as an ester that is converted by hydrolysis in vivo to the hydroxy compound. Suitable esters that may be converted in vivo into hydroxy compounds include acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylenebis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyletartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfonates, quinates, esters of amino acids, and the like. Similarly, an inhibitor comprising an amine group may be administered as an amide that is converted by hydrolysis in vivo to the amine compound.

"Protected derivatives" means derivatives of inhibitors in which a reactive site or sites are blocked with protecting groups. Protected derivatives are useful in the preparation of inhibitors or in themselves may be active as inhibitors. A comprehensive list of suitable protecting groups can be found in T. W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Substituted or unsubstituted" means that a given moiety may consist of only hydrogen substituents through available valencies (unsubstituted) or may further comprise one or more non-hydrogen substituents through available valencies (substituted) that are not otherwise specified by the name of the given moiety. For example, isopropyl is an example of an ethylene moiety that is substituted by —CH₃. In general, a non-hydrogen substituent may be any substituent that may be bound to an atom of the given moiety that is specified to be substituted. Examples of substituents include, but are not limited to, aldehyde, alicyclic, aliphatic, alkyl, alkylene, alkylidene, amide, amino, aminoalkyl, aromatic, aryl, bicycloalkyl, bicycloaryl, carbamoyl, carbocyclyl, carboxyl, carbonyl group, cycloalkyl, cycloalkylene, ester, halo, heterobicycloalkyl, heterocycloalkylene, heteroaryl, hetero-

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bicycloaryl, heterocycloalkyl, oxo, hydroxy, iminoketone, ketone, nitro, oxaalkyl, and oxoalkyl moieties, each of which may optionally also be substituted or unsubstituted.

"Sulfinyl" means the radical —SO—. It is noted that the sulfinyl radical may be further substituted with a variety of substituents to form different sulfinyl groups including sulfinic acids, sulfonamides, sulfinyl esters, and sulfoxides.

"Sulfonyl" means the radical —SO₂—. It is noted that the sulfonyl radical may be further substituted with a variety of substituents to form different sulfonyl groups including sulfonic acids, sulfonamides, sulfonate esters, and sulfones.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thiocarbonyl" means the radical —CS—. It is noted that the thiocarbonyl radical may be further substituted with a variety of substituents to form different thiocarbonyl groups including thioacids, thioamides, thioesters, and thicketones.

"Treatment" or "treating" means any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the disease (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the disease (i.e., reversing the pathology and/or symptomatology).

It is noted in regard to all of the definitions provided herein that the definitions should be interpreted as being open ended in the sense that further substituents beyond those specified may be included. Hence, a C₁ alkyl indicates that there is one carbon atom but does not indicate what are the substituents on the carbon atom. Hence, a C₁ alkyl comprises methyl (i.e., —CH₃) as well as —R_aR_bR_c where R_a, R_b, and R_c may each independently be hydrogen or any other substituent where the atom attached to the carbon is a heteroatom or cyano. Hence, CF₃, CH₂OH and CH₂CN, for example, are all C₁ alkyls.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds, compositions, kits and articles of manufacture that may be used to inhibit dipeptidyl peptidases IV (referred to herein as DPP-IV).

DPP-IV (EC.3.4.14.5 also known as DPP4, DP4, DAP-IV, adenosine deaminase complexing protein 2, adenosine deaminase binding protein (ADAbp) or CD26) is a 766 residue, 240 kDa protein that is a highly specific membrane bound non-classical serine aminopeptidase. DPP-IV has a serine type mechanism of protease activity, cleaving off dipeptides from the amino-terminus of peptides with proline or alanine at the penultimate position. In addition the slow release of dipeptides of the type X-Gly or X-Ser is reported for some naturally occurring peptides. DPP-IV is constitutively expressed on epithelial and endothelial cells of a variety of different tissues (intestine, liver, lung, kidney and placenta), and is also found in body fluids. DPP-IV is also expressed on circulating T-lymphocytes and has been shown to be synonymous with the cell-surface antigen, CD-26. The wild-type form of full length DPP-IV is described in GenBank Accession Number NM_001935 ("Dipeptidyl peptidase IV (CD 26) gene expression in enterocyte-like colon cancer cell lines HT-29 and Caco-2. Cloning of the complete human coding sequence and changes of dipeptidyl peptidase IV mRNA levels during cell differentiation", Darmoul, D.,

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Lacasa, M., Baricault, L., Marguet, D., Sapin, C., Trotot, P., Barbat, A. and Trugnan, G., J. Biol. Chem., 267 (7), 4824-4833, 1992.

DPP-IV is a member of the S9 family of serine proteases, more particularly the S9B family. Other members of the S9 family include, but are not limited to:

Subfamily S9A: Dipeptidyl-peptidase; Oligopeptidase B (EC 3.4.21.83); Oligopeptidase B; Prolyl oligopeptidase (EC 3.4.21.26);

Subfamily S9B: Dipeptidyl aminopeptidase A; Dipeptidyl aminopeptidase B; Dipeptidyl-peptidase IV (EC 3.4.14.5); Dipeptidyl-peptidase V Fibroblast activation protein alpha subunit; Seprase

Subfamily S9C: Acylaminoacyl-peptidase (EC 3.4.19.1)

It is noted that the compounds of the present invention may also possess inhibitory activity for other S9 family members and thus may be used to address disease states associated with these other family members.

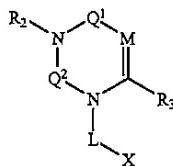
1. Crystal Structure of DPP-IV

Syrrx, Inc. (San Diego, Calif.) recently solved the crystal structure of DPP-IV. Knowledge of the crystal structure was used to guide the design of the DPP-IV inhibitors provided herein.

FIG. 1 illustrates a ribbon diagram overview of the structure of DPP-IV, highlighting secondary structural elements of the protein. DPP-IV is a cylindrical shaped molecule with an approximate height of 70 Å and a diameter of 60 Å. The catalytic triad of DPP-IV (Ser642, Asp720 and His752) is illustrated in the center of the FIGURE by a "ball and stick" representation. This triad of amino acids is located in the peptidase domain or catalytic domain of DPP-IV. The catalytic domain is covalently linked to the β-propeller domain. The catalytic domain of DPP-IV includes residues 1-67 and 511-778. The catalytic domain of DPP-IV adopts a characteristic α/β hydrolase fold. The core of this domain contains an 8-stranded β-sheet with all strands being parallel except one. The α-sheet is significantly twisted and is flanked by three α-helices on one side and five α-helices on the other. The topology of the β-strands is 1, 2, -1x, 2x and (1x) (J. S. Richardson: The anatomy and taxonomy of protein structure; (1981) *Adv. Protein Chem.* 269, 15076-15084.). A number of residues were identified that contribute to the shape and charge characteristics of the active site. Knowledge of these residues has been an important contribution to the design of DPP-IV inhibitors of the present invention.

2. DPP-IV Inhibitors

In one embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

M is N or CR₄;

Q¹ and Q² are each independently selected from the group consisting of CO, CS, SO, SO₂, and C=NR₉;

R₂ is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl,

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alkyl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R₃ is selected from the group consisting of perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

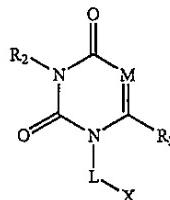
R₄ is hydrogen or is selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R₅ is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



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wherein

M is N or CR₄;

R₂ is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R₃ is selected from the group consisting of perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

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loxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent L:

In one variation of the above embodiments, DPP-IV inhibitors of the present invention comprise compounds wherein the 1, 2 or 3 atoms of L providing the separation consist of carbon atoms. In another variation, the 1, 2 or 3 atoms of L providing the separation are selected from the group of linkers consisting of at least one oxygen or at least one nitrogen atom. In yet another variation, L separates X from the ring atom by one atom.

In one particular variation of the above embodiments, L is selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{CH}_2\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{CH}_2-\text{C}(\text{O})\text{CH}_2-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{O}-$, $-\text{OCH}_2-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{N}(\text{CH}_3)-$, $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{NHCH}_2-$, $-\text{NHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{NCH}_3-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{NCH}_3-$, $-\text{NHC}(\text{O})\text{CH}_2-$, $-\text{C}(\text{O})\text{NHCH}_2-$, $-\text{C}(\text{O})\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{NHC}(\text{O})-$, $-\text{CH}_2\text{C}(\text{O})\text{NH}-$, $-\text{NHCH}_2\text{C}(\text{O})-$, $-\text{S}-$, $-\text{SCH}_2-$, $-\text{CH}_2\text{S}-$, $-\text{SCH}_2\text{CH}_2-$, $-\text{CH}_2\text{SCH}_2-$, $-\text{CH}_2\text{CH}_2\text{S}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{SCH}_2-$, $-\text{CH}_2\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{CH}_2\text{S}-$, and $-\text{CH}_2\text{SC}(\text{O})-$, each substituted or unsubstituted.

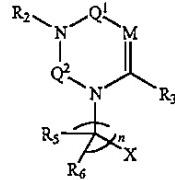
In another particular variation of the above embodiments, L is selected from the group consisting of $-\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{CH}_2\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{CH}_2-\text{C}(\text{O})\text{CH}_2-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, each substituted or unsubstituted.

In one particular variation of the above embodiments, $-L-X$ taken together is selected from the group consisting of $-(\text{CH}_2)-(2\text{-cyano})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-cyano})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-hydroxy})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-hydroxy})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-alkenyl})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-alkenyl})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-alkynyl})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-alkynyl})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-methoxy})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-methoxy})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-nitro})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-nitro})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-carboxy})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-carboxy})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-carboxamido})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-carboxamido})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-sulfonamido})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-sulfonamido})\text{phenyl}$, $-(\text{CH}_2)-(2\text{-tetrazolyl})\text{phenyl}$, $-(\text{CH}_2)-(3\text{-tetrazolyl})\text{phenyl}$, and $-(\text{CH}_2)-(2\text{-aminomethyl})$

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phenyl; $-(\text{CH}_2)-(3\text{-aminomethyl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-hydroxymethyl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-hydroxymethyl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-phenyl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-phenyl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-halo})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-halo})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-CONH}_2)\text{phenyl}$; $-(\text{CH}_2)-(3\text{-CONH}_2)\text{phenyl}$; $-(\text{CH}_2)-(2\text{-CONH}(\text{C}_{1-7})\text{alkyl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-CONH}(\text{C}_{1-7})\text{alkyl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-CO}_2(\text{C}_{1-7})\text{alkyl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-CO}_2(\text{C}_{1-7})\text{alkyl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-NH}_2)\text{phenyl}$; $-(\text{CH}_2)-(3\text{-NH}_2)\text{phenyl}$; $-(\text{CH}_2)-(2\text{-}(\text{C}_{3-7})\text{alkyl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-}(\text{C}_{3-7})\text{alkyl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-}(\text{C}_{3-7})\text{cycloalkyl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-}(\text{C}_{3-7})\text{cycloalkyl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-aryl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-aryl})\text{phenyl}$; $-(\text{CH}_2)-(2\text{-heteroaryl})\text{phenyl}$; $-(\text{CH}_2)-(3\text{-heteroaryl})\text{phenyl}$; $-(\text{CH}_2)\text{-2-bromo-5-fluoro phenyl}$; $-(\text{CH}_2)\text{-2-chloro-5-fluoro phenyl}$; $-(\text{CH}_2)\text{-2,5-dichloro phenyl}$; $-(\text{CH}_2)\text{-2,5-difluoro phenyl}$; $-(\text{CH}_2)\text{-2,5-dibromo phenyl}$; $-(\text{CH}_2)\text{-2-bromo-3,5-difluoro phenyl}$; $-(\text{CH}_2)\text{-2,3,5-trifluoro phenyl}$; $-(\text{CH}_2)\text{-2,3,5,6-tetrafluorophenyl}$; $-(\text{CH}_2)\text{-2-bromo-3,5,6-trifluoro phenyl}$; $-(\text{CH}_2)\text{-2-chloro-3,5,6-trifluoro phenyl}$; $-(\text{CH}_2)\text{-2-cyano-3,5,6-trifluoro phenyl}$; $-(\text{CH}_2)\text{-2-heterocycloalkyl})\text{phenyl}$; and $-(\text{CH}_2)-(3\text{-heterocycloalkyl})\text{phenyl}$, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

n is 1, 2, or 3;

M is N or CR_4 ;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2 , and $\text{C}=\text{NR}_9$;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R_4 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl,

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hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

each R₅ and R₆ is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C₁₋₁₀)alkyl, a substituted or unsubstituted (C₁₋₁₀)alkoxy, cyano, and halo, or where R₅ and R₆ are taken together to form a ring;

R₉ is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycaryl, and heterobicycaryl, each substituted or unsubstituted; and

X is selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent X:

In regard to particular variations of the present invention, there is provided compounds wherein X is a substituted or unsubstituted (C₃₋₇)cycloalkyl. According to each of the above variations, the invention provides compounds wherein X is a substituted or unsubstituted (C₃₋₇)heterocycloalkyl, or wherein X is a substituted or unsubstituted aryl.

Further, according to each of the above variations, the invention provides compounds wherein X is a substituted or unsubstituted phenyl, or wherein X is a substituted or unsubstituted heteroaryl. In another variation according to the above variation, X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring.

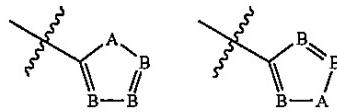
According to the above variations, there is provided compounds wherein X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, cyano, nitro, halo, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted. In another variation of the above, X is a substituted or unsubstituted halophenyl or dihalophenyl. In yet another variation, X is a substituted or unsubstituted haloaryl, haloheteroaryl, dihaloaryl or dihaloheteroaryl.

According to the above variations, X is selected from the group consisting of (2-cyano)phenyl; (3-cyano)phenyl; (2-hydroxy)phenyl; (3-hydroxy)phenyl; (2-alkenyl)phenyl; (3-alkenyl)phenyl; (2-alkynyl)phenyl; (3-alkynyl)phenyl; (2-methoxy)phenyl; (3-methoxy)phenyl; (2-nitro)phenyl; (3-nitro)phenyl; (2-carboxy)phenyl; (3-carboxy)phenyl; —(CH₂)-(2-carboxamido)phenyl; (3-carboxamido)phenyl; (2-sulfonamido)phenyl; (3-sulfonamido)phenyl; (2-tetrazolyl)phenyl; (3-tetrazolyl)phenyl; (2-aminomethyl)phenyl; (3-aminomethyl)phenyl; (2-hydroxymethyl)phenyl; (3-hydroxymethyl)phenyl; (2-phenyl)phenyl; (3-phenyl)phenyl; (2-halo)phenyl; (3-halo)phenyl; (2-CONH₂)phenyl; (3-COHNH₂)phenyl; (2-COCONH(C₁₋₇)alkyl)phenyl; (3-COCONH(C₁₋₇)alkyl)phenyl; (2-CO₂(C₁₋₇)alkyl)phenyl; (3-CO₂(C₁₋₇)alkyl)phenyl; (2-NH₂)phenyl; (3-NH₂)phenyl; (2-(C₃₋₇)alkyl)phenyl; (3-(C₃₋₇)alkyl)phenyl; (2-(C₃₋₇)cycloalkyl)phenyl; (3-(C₃₋₇)cycloalkyl)phenyl; (2-aryl)phenyl; (3-aryl)phenyl; (2-heteroaryl)phenyl; (3-heteroaryl)phenyl;

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2-bromo-5-fluoro phenyl; 2-chloro-5-fluoro phenyl; 2-cyano-5-fluoro phenyl; 2,5-dichloro phenyl; 2,5-difluoro phenyl; 2-chloro-3,5-difluoro phenyl; 2,3,5-trifluoro phenyl; 2,3,5,6-tetrafluorophenyl; 2-bromo-3,5,6-trifluoro phenyl; 2-chloro-3,5,6-trifluoro phenyl; 2-cyano-3,5-difluoro phenyl; 2-cyano-3,5,6-trifluoro phenyl; (2-heterocycloalkyl)phenyl; and (3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

In regard to the above particular variations, the invention also include compounds wherein X is selected from the group consisting of



wherein

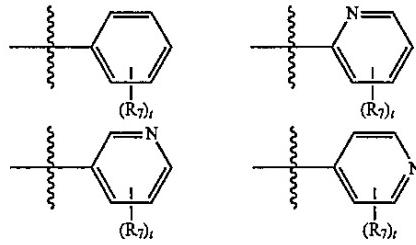
A is S, O or NR₂₄;

B is CR₂₂ or N;

R₂₃ is independently selected from the group consisting of hydrogen, halo, perhalo(C₁₋₁₀)alkyl, amino, thio, cyano, CF₃, nitro, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₈₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R₂₄ is independently selected from the group consisting of hydrogen, perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₈₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

In one variation of the above embodiments and variations, X is selected from the group consisting of



wherein

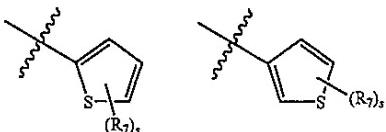
t is 0, 1, 2, 3, 4 or 5; and

each R_t is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

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In another variation of the above compounds, X is selected from the group consisting of



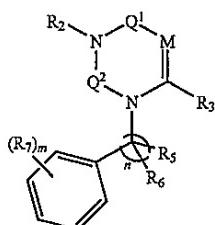
wherein

s is 0, 1, 2, or 3; and

each R₇ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In one particular variation of the above compounds, R₇ is independently selected from the group consisting of -cyano, -methoxy, -nitro, -carboxy, -sulfonamido, -tetrazolyl, -aminomethyl, -hydroxymethyl, -phenyl, -halo, —CONH₂, —CONH(C₁₋₇)alkyl, —CO₂(C₁₋₇)alkyl, —NH₂, —OH, —(C₁₋₅)alkyl, -alkenyl, -alkynyl, (C₁₋₅)cycloalkyl, aryl, heteroaryl, and heterocycloalkyl, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

m is 0, 1, 2, 3, 4, or 5;

n is 1, 2, or 3;

M is N or CR₄;

Q¹ and Q² are each independently selected from the group consisting of CO, CS, SO, SO₂, and C=NR₉;

R₂ is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R₃ is selected from the group consisting of perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfi-

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nyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R₄ is hydrogen or is selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, 5 cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

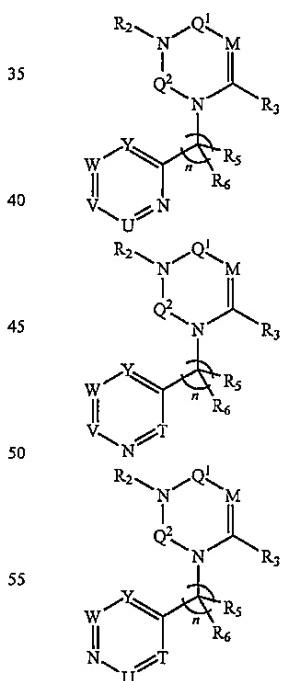
each R₅ and R₆ is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C₁₋₁₀)alkyl, a substituted or unsubstituted (C₁₋₁₀)alkoxy, cyano, and halo, or where R₅ and R₆ are taken together to form 15 a ring;

each R₇ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

R₉ is hydrogen or is selected from the group consisting of 25 alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:

30 a member selected from the group consisting of



wherein

n is 1, 2, or 3;

M is N or CR₄;

each of T, U, V, W and Y is independently nitrogen or CR₁₆, provided that no more than two of T, U, V, W and Y are nitrogen;

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Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2 , and $C=NR_g$;

R₂ is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

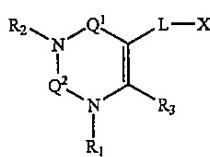
R₄ is hydrogen or is selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C₁₋₃)alkyl, thiocabonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

each R₅ and R₆ is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C₁₋₁₀)alkyl, a substituted or unsubstituted (C₁₋₁₀)alkoxy, cyano, and halo, or where R₅ and R₆ are taken together to form a ring;

R_3 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

each R₁₋₆ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2 , and $C=NR_9$;

R₁ is hydrogen or is selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl,

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hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of $(C_{1-10})alkyl$, $(C_{3-12})cycloalkyl$, $(C_3-t_2)cycloalkyl(C_{1-5})alkyl$, hetero $(C_{3-12})cycloalkyl(C_{1-5})alkyl$, hetero $(C_{3-12})cycloalkyl$, aryl $(C_{1-10})alkyl$, heteroaryl $(C_{1-5})alkyl$, $(C_{9-12})bicycloaryl$, hetero $(C_{4-12})bicycloaroyl$, hetero $(C_{4-12})bicycloaryl(C_{1-5})alkyl$, carbonyl $(C_{1-3})alkyl$, thiocarbonyl $(C_{1-3})alkyl$, sulfonyl $(C_{1-3})alkyl$, sulfinyl $(C_{1-3})alkyl$, imino $(C_{1-3})alkyl$, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

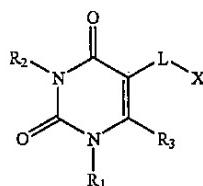
R_3 is selected from the group consisting of perhalo(C_{1-10})
 15 alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, ary-
 lalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl,
 thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})
 20 alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroary-
 loxy, carbonyl group, imino group, sulfonyl group and sulfi-
 nyl group, each substituted or unsubstituted, and a substituted
 or unsubstituted 3, 4, 5, 6 or 7 membered ring;

²⁵ R₉ is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

30 X is selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

R₁ is hydrogen or is selected from the group consisting of
 55 halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl,
 cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl,
 heteroaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl,
 sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl,
 hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group,
 60 imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R₂ is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, 65 aryl(C₁₋₁₀)alkyl, heteroaryl(C₃₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, alkyl carbonyl (C₁₋₅)alkyl thiocarbonyl (C₁₋₅)alkyl, sulfonyl

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(C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent L:

In one variation of the present invention, there is provided compounds wherein the 1, 2 or 3 atoms of L providing the separation consist of carbon atoms. In another variation, the 1, 2 or 3 atoms of L providing the separation are selected from the group of linkers consisting of at least one oxygen or at least one nitrogen atom. In one particular variation, L separates X from the ring atom by one atom.

In regard to particular variation of the present invention, L is selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{CH}_2\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{CH}_2-\text{C}(\text{O})\text{CH}_2-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{O}-$, $-\text{OCH}_2-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{N}(\text{CH}_3)-$, $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{NHCH}_2-$, $-\text{NHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{NCH}_3-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{NCH}_3-$, $-\text{NHC}(\text{O})\text{CH}_2-$, $-\text{C}(\text{O})\text{NHCH}_2-$, $-\text{C}(\text{O})\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{NHC}(\text{O})-$, $-\text{CH}_2\text{C}(\text{O})\text{NH}-$, $-\text{NHCH}_2\text{C}(\text{O})-$, $-\text{S}-$, $-\text{SCH}_2-$, $-\text{CH}_2\text{S}-$, $-\text{SCH}_2\text{CH}_2-$, $-\text{CH}_2\text{SCH}_2-$, $-\text{CH}_2\text{CH}_2\text{S}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{SCH}_2-$, $-\text{CH}_2\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{CH}_2\text{S}-$, and $-\text{CH}_2\text{SC}(\text{O})-$, each substituted or unsubstituted.

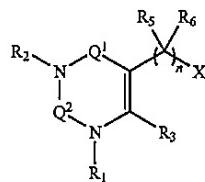
In regard to another variation of the above compounds, L is selected from the group consisting of $-\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{CH}_2\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{CH}_2-\text{C}(\text{O})\text{CH}_2-$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, each substituted or unsubstituted.

In another variation of the above compounds, $-L-X$ taken together is selected from the group consisting of $-(CH_2)-(2\text{-cyano})phenyl$; $-(CH_2)-(3\text{-cyano})phenyl$; $-(CH_2)-(2\text{-hydroxy})phenyl$; $-(CH_2)-(3\text{-hydroxy})phenyl$; $-(CH_2)-(2\text{-alkenyl})phenyl$; $-(CH_2)-(3\text{-alkenyl})phenyl$; $-(CH_2)-(2\text{-alkynyl})phenyl$; $-(CH_2)-(3\text{-alkynyl})phenyl$; $-(CH_2)-(2\text{-methoxy})phenyl$; $-(CH_2)-(3\text{-methoxy})phenyl$; $-(CH_2)-(2\text{-nitro})phenyl$; $-(CH_2)-(3\text{-nitro})phenyl$; $-(CH_2)-(2\text{-carboxy})phenyl$; $-(CH_2)-(3\text{-carboxy})phenyl$; $-(CH_2)-(2\text{-carboxamido})phenyl$; $-(CH_2)-(3\text{-carboxamido})phenyl$; $-(CH_2)-(2\text{-sulfonamido})phenyl$; $-(CH_2)-(3\text{-sulfonamido})phenyl$; $-(CH_2)-(2\text{-tetrazolyl})phenyl$; $-(CH_2)-(3\text{-tetrazolyl})phenyl$; $-(CH_2)-(2\text{-aminomethyl})phenyl$; $-(CH_2)-$

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(3-aminomethyl)phenyl; —(CH₂)-(2-hydroxymethyl)phenyl; —(CH₂)-(3-hydroxymethyl)phenyl; —(CH₂)-(2-phenyl)phenyl; —(CH₂)-(3-phenyl)phenyl; —(CH₂)-(2-halo)phenyl; —(CH₂)-(3-halo)phenyl; —(CH₂)-(2-CO NH₂)phenyl; —(CH₂)-(3-CO NH₂)phenyl; —(CH₂)-(2-CO NH(C₁₋₇)alkyl)phenyl; —(CH₂)-(3-CO NH(C₁₋₇)alkyl)phenyl; —(CH₂)-(2-CO₂(C₁₋₇)alkyl)phenyl; —(CH₂)-(3-CO₂(C₁₋₇)alkyl)phenyl; —(CH₂)-(2-NH₂)phenyl; —(CH₂)-(3-NH₂)phenyl; —(CH₂)-(2-(C₃₋₇)alkyl)phenyl; —(CH₂)-(3-(C₃₋₇)alkyl)phenyl; —(CH₂)-(2-(C₃₋₇)cycloalkyl)phenyl; —(CH₂)-(3-(C₃₋₇)cycloalkyl)phenyl; —(CH₂)-(2-aryl)phenyl; —(CH₂)-(3-aryl)phenyl; —(CH₂)-(2-heteroaryl)phenyl; —(CH₂)-(3-heteroaryl)phenyl; —(CH₂)-2-bromo-5-fluoro phenyl; —(CH₂)-2-chloro-5-fluoro phenyl; —(CH₂)-2-cyano-5-fluoro phenyl; —(CH₂)-2,5-dichloro phenyl; —(CH₂)-2,5-difluoro phenyl; —(CH₂)-2,5-dibromo phenyl; —(CH₂)-2-bromo-3,5-difluoro phenyl; —(CH₂)-2-chloro-3,5-difluoro phenyl; —(CH₂)-2,3,5-trifluoro phenyl; —(CH₂)-2,3,5,6-tetrafluorophenyl; —(CH₂)-2-bromo-3,5,6-trifluoro phenyl; —(CH₂)-2-chloro-3,5,6-trifluoro phenyl; —(CH₂)-2-cyano-3,5,6-trifluoro phenyl; —(CH₂)-(2-heterocycloalkyl)phenyl; and —(CH₂)-(3-heterocycloalkyl)phenyl, each substituted as indicated.

25 In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

is 1, 2, or 3;

Q^1 and Q^2 are each independently selected from the group consisting of CO, CS, SO, SO_2 , and $C=NR_9$;

R_1 is hydrogen or is selected from the group consisting of halo, perhalo(C_{1-10})alkyl, amino, cyano, thio, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of $(C_{1-10})alkyl$, $(C_{3-12})cycloalkyl$, $(C_{3-12})cycloalkyl(C_{1-5})alkyl$, hetero $(C_{3-12})cycloalkyl(C_{1-5})alkyl$, hetero $(C_{3-12})cycloalkyl$, aryl $(C_{1-10})alkyl$, heteroaryl $(C_{1-5})alkyl$, $(C_{9-12})bicycloaryl$, hetero $(C_{4-12})bicycloaryl$, hetero $(C_{4-12})bicycloaryl(C_{1-5})alkyl$, carbonyl $(C_{1-3})alkyl$, thiocarbonyl $(C_{1-3})alkyl$, sulfonyl $(C_{1-3})alkyl$, sulfinyl $(C_{1-3})alkyl$, imino $(C_{1-3})alkyl$, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

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each R₅ and R₆ is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C₁₋₁₀)alkyl, a substituted or unsubstituted (C₁₋₁₀)alkoxy, cyano, and halo, or where R₅ and R₆ are taken together to form a ring;

R₅ is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

X is selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent X:

According to the above variations, the invention provides compounds wherein X is a substituted or unsubstituted (C₃₋₇)cycloalkyl. In another particular variation of the above compounds, wherein X is a substituted or unsubstituted (C₃₋₇)heterocycloalkyl, wherein X is a substituted or unsubstituted aryl, or wherein X is a substituted or unsubstituted phenyl. In another particular variation, X is a substituted or unsubstituted heteroaryl.

In one particular variation of the above compounds, X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring. In one variation of the above compounds, X is a ring having a non-hydrogen substituent at a 2 or 3 position of the ring selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, cyano, nitro, halo, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

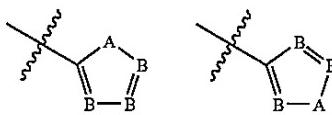
In another particular variation, X is a substituted or unsubstituted halophenyl or dihalophenyl. In yet another particular variation, there is provided compounds wherein X is a substituted or unsubstituted haloaryl, haloheteroaryl, dihaloaryl or dihaloheteroaryl.

In regard to particular variations, the present invention provides compounds wherein X is selected from the group consisting of (2-cyano)phenyl; (3-cyano)phenyl; (2-hydroxy)phenyl; (3-hydroxy)phenyl; (2-alkenyl)phenyl; (3-alkenyl)phenyl; (2-alkynyl)phenyl; (3-alkynyl)phenyl; (2-methoxy)phenyl; (3-methoxy)phenyl; (2-nitro)phenyl; (3-nitro)phenyl; (2-carboxy)phenyl; (3-carboxy)phenyl; -(CH₂)-(2-carboxamido)phenyl; (3-carboxamido)phenyl; (2-sulfonamido)phenyl; (3-sulfonamido)phenyl; (2-tetrazolyl)phenyl; (3-tetrazolyl)phenyl; (2-aminomethyl)phenyl; (3-aminomethyl)phenyl; (2-hydroxymethyl)phenyl; (2-phenyl)phenyl; (3-phenyl)phenyl; (2-halo)phenyl; (3-halo)phenyl; (2-CONH₂)phenyl; (3-CONH₂)phenyl; (2-CONH(C₁₋₇)alkyl)phenyl; (3-CONH(C₁₋₇)alkyl)phenyl; (2-CO₂(C₁₋₇)alkyl)phenyl; (3-CO₂(C₁₋₇)alkyl)phenyl; (2-NH₂)phenyl; (3-NH₂)phenyl; (2-(C₃₋₇)alkyl)phenyl; (3-(C₃₋₇)alkyl)phenyl; (2-(C₃₋₇)cycloalkyl)phenyl; (3-(C₃₋₇)cycloalkyl)phenyl; (2-aryl)phenyl; (3-aryl)phenyl; (2-heteroaryl)phenyl; (3-heteroaryl)phenyl; 2-bromo-5-fluoro phenyl; 2-chloro-5-fluoro phenyl; 2-cyano-5-fluoro phenyl; 2,5-dichloro phenyl; 2,5-difluoro phenyl;

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nyl; 2,5-dibromo phenyl; 2-bromo-3,5-difluoro phenyl; 2-chloro-3,5-difluoro phenyl; 2,3,5-trifluoro phenyl; 2,3,5,6-tetrafluorophenyl; 2-bromo-3,5,6-trifluoro phenyl; 2-chloro-3,5,6-trifluoro phenyl; 2-cyano-3,5-difluoro phenyl; 2-cyano-3,5,6-trifluoro phenyl; (2-heterocycloalkyl)phenyl; and (3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

In one variation of the above compounds, X is selected from the group consisting of



wherein

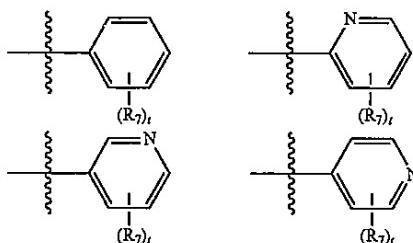
20 A is S, O or NR₂₄;

B is CR₂₃ or N;

R₂₃ is independently selected from the group consisting of hydrogen, halo, perhalo(C₁₋₁₀)alkyl, amino, thio, cyano, CF₃, 25 nitro, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₈₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, amino-30 sulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

R₂₄ is independently selected from the group consisting of hydrogen, perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₈₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

In another particular variation of the above compounds, X is selected from the group consisting of



wherein

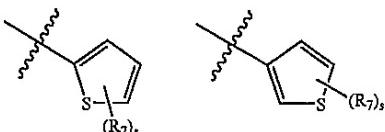
t is 0, 1, 2, 3, 4, or 5; and

each R₇ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

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In yet another variation, X is selected from the group consisting of



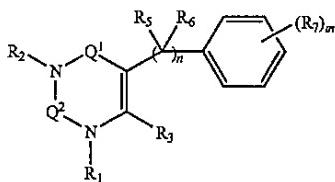
wherein

s is 0, 1, 2, or 3; and

each R₇ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In one particular variation of the above compounds, R₇ is independently selected from the group consisting of -cyano, -methoxy, -nitro, -carboxy, -sulfonamido, -tetrazolyl, -aminomethyl, -hydroxymethyl, -phenyl, -halo, —CONH₂, —CONH(C₁₋₇)alkyl, —CO₂(C₁₋₇)alkyl, —NH₂, —OH, —(C₁₋₅)alkyl, -alkenyl, -alkynyl, (C₁₋₅)cycloalkyl, aryl, heteroaryl, and heterocycloalkyl, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:



wherein

m is 0, 1, 2, 3, 4 or 5;

n is 1, 2, or 3;

Q¹ and Q² are each independently selected from the group consisting of CO, CS, SO, SO₂, and C=NR₉;

R₁ is hydrogen or is selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R₂ is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

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R₃ is selected from the group consisting of perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl,

5 alkyl, imino (C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

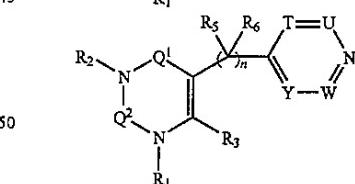
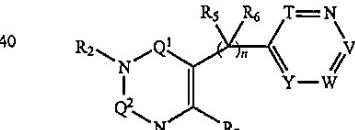
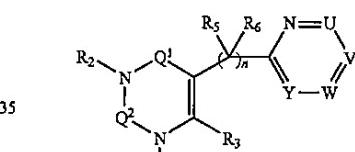
each R₅ and R₆ is independently hydrogen or is selected 10 from the group consisting of a substituted or unsubstituted (C₁₋₁₀)alkyl, a substituted or unsubstituted (C₁₋₁₀)alkoxy, cyano, and halo, or where R₅ and R₆ are taken together to form a ring;

each R₇ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

20 R₉ is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted.

In another embodiment, DPP-IV inhibitors of the present invention include compounds comprising:

a member selected from the group consisting of



wherein

n is 1, 2, or 3;

Q¹ and Q² are each independently selected from the group consisting of CO, CS, SO, SO₂, and C=NR₉;

each of T, U, V, W and Y is independently nitrogen or CR₁₆, provided that no more than two of T, U, V, W and Y are nitrogen;

65 R₁ is hydrogen or is selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl,

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hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, imino(C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R_3 is selected from the group consisting of perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, imino(C_{1-3})alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

each R_5 and R_6 is independently hydrogen or is selected from the group consisting of a substituted or unsubstituted (C_{1-10})alkyl, a substituted or unsubstituted (C_{1-10})alkoxy, cyano, and halo, or where R_5 and R_6 are taken together to form a ring;

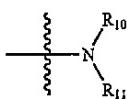
R_9 is hydrogen or is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, bicycloaryl, and heterobicycloaryl, each substituted or unsubstituted; and

each R_{16} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3 , (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent R_3 :

In regard to each of the above embodiments and variations, the present invention provides compounds wherein R_3 is selected from the group consisting of amino, (C_{1-10})alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, and heteroaryl, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring.

Further, according to each of the above embodiments and variations, the present invention also provides compounds wherein R_3 comprises the formula

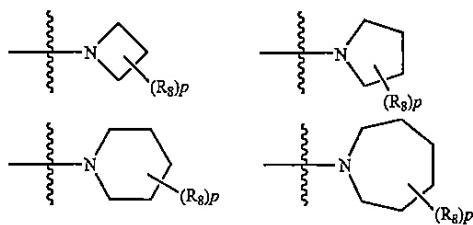


wherein R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, and sulfinyl group, each substituted or unsubstituted, or R_{10} and R_{11} are taken together to form a 4, 5, 6, or 7 membered ring, each substituted or unsubstituted.

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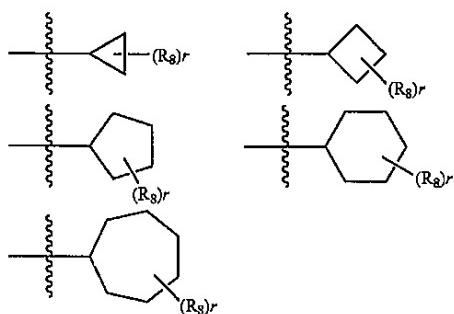
According to another variation of each of the above embodiments and variations, R_3 is a substituted or unsubstituted 3, 4, 5, 6, or 7 membered ring, wherein R_3 is a substituted or unsubstituted 3, 4, 5, 6, or 7 membered cycloalkyl, or wherein R_3 is a substituted or unsubstituted 4, 5, 6, or 7 membered heterocycloalkyl. In another variation of the above, R_3 is a substituted or unsubstituted aryl, or wherein R_3 is a substituted or unsubstituted heteroaryl.

In one particular variation of the above embodiments and variations, R_3 is selected from the group consisting of



wherein p is 0-12 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3 , cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In another particular variation of the above embodiments and variations, R_3 is selected from the group consisting of



wherein r is 0-13 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3 , cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

According to each of the above embodiments and variations, DPP-IV inhibitors of the present invention may comprise compounds wherein R_3 is a substituted or unsubstituted heteroaryl selected from the group consisting of furan, thiophene, pyrrole, pyrazole, triazole, isoxazole, oxazole, thiazole, isothiazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, imidazole, benzimidazole, indole, isoindole, quinoline, isoquinoline, cinnoline,

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quinazoline, naphthyridine, pyridopyridine, quinoxaline, phthalazine, and benzothiazole, each substituted or unsubstituted.

Further, according to the above embodiments and variations, R₃ may be selected from the group consisting of (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl (C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, and hetero(C₄₋₁₂)bicycloaryl, each substituted or unsubstituted. In another variation, R₃ is a substituted or unsubstituted (C₃₋₇)cycloalkyl ring, optionally comprising O, N(O), N, S, SO, SO₂ or a carbonyl group in the ring.

According to each of the above embodiments and variations, R₃ may also be substituted such that R₃ comprises a substituent selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, and a heteroaryl comprising a nitrogen ring atom.

In particular variations of the present invention, R₃ comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein. In one variation, the basic nitrogen of R₃ is separated from the ring atom to which R₃ is attached by between 1-5 atoms. In another variation, the basic nitrogen atom forms part of a primary, secondary or tertiary amine. In yet another variation, the basic nitrogen atom is a nitrogen ring atom of a heterocycloalkyl or a heteroaryl.

In one variation of each of the embodiments of the present invention, R₃ includes a basic nitrogen that is capable of interacting with a carboxylic acid side chain of a residue in the DP-4 active site and thus contributes to the binding affinity of the compound to DP-4. Based on co-crystal structures obtained by Applicants, the observed interaction between the basic nitrogen substituent and the carboxylic acid appears to be via hydrogen bonding or by the formation of a salt bridge.

The basic nitrogen of R₃ in this variation that provides the desired carboxylic acid side chain interaction is not typically directly attached to the ring atom to which R₃ is attached. In this regard, the basic nitrogen may be viewed as a substituent of the overall R₃ moiety. For example, in the case where R₃ is 3-amino-piperidinyl-1-yl, the basic nitrogen is the 3-amino group and not the nitrogen of the piperidine ring. Thus, R₃ may be viewed as a substituted piperidine ring further comprising an amine as a basic nitrogen substituent. In a particular variation, the basic nitrogen of R₃ is optionally separated from the ring atom to which R₃ is attached by between 1-5 atoms.

The basic nitrogen atom moiety of R₃ may optionally be selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, a heteroaryl comprising a nitrogen ring atom, as well as other nitrogen containing moieties where the nitrogen can act as a Lewis base. In addition to basic nitrogen containing moieties, it is envisioned that other Lewis bases, such as oxygen with basic lone pairs, may be capable of interacting with a carboxylic acid side chain of a residue in the DP-4 active site.

In certain embodiments, R₃ is said to be further substituted with one or more R₈ substituents. It is noted that at least one of the R₈ substituents may comprise the basic nitrogen atom capable of providing the interaction with the carboxylic acid side chain. In this regard, R₈ may optionally comprise a moiety selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, a heteroaryl comprising a nitrogen ring atom, as well as other nitrogen containing moieties where the nitrogen can act as a Lewis base.

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Particular examples of moieties with basic nitrogens according to this variation include, but are not limited to —NH₂, —NH(C₁₋₅ alkyl), —N(C₁₋₅ alkyl)₂, piperazine, imidazole, and pyridine. Additional particular R₃ groups that comprise a basic nitrogen include, but are not limited to 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 3-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each optionally further substituted.

15 In regard to a particular variation, at least one R₈ comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein. In another particular variation, the basic nitrogen atom forms part of a primary, secondary or tertiary amine. In yet another variation of the above compounds, the basic nitrogen atom is a nitrogen ring atom of a heterocycloalkyl comprising a nitrogen ring atom or a heteroaryl comprising a nitrogen ring atom.

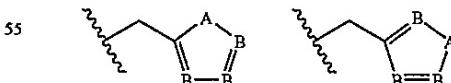
15 In one variation of each of the embodiments of the present invention, at least one R₈ is a primary, secondary or tertiary amine. In another variation, at least one R₈ is a substituted or unsubstituted heterocycloalkyl comprising a nitrogen ring atom or a substituted or unsubstituted heteroaryl comprising a nitrogen ring atom. In yet another particular variation, at least one R₈ is selected from the group consisting of —NH₂, —NH(C₁₋₅ alkyl), —N(C₁₋₅ alkyl)₂, piperazine, imidazole, and pyridine.

According to each of the above embodiments and variations, R₃ is selected from the group consisting of 3-amino-35 piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 3-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each substituted or unsubstituted.

45 In one particular variation, at least one of Q¹ and Q² is CO. In another variation of the above compounds, Q¹ and Q² are CO.

Substituent M:

In another particular variation, the present invention provides compounds wherein M is nitrogen. In yet another particular variation, M is CR₄ and where R₄ is selected from the group consisting of



55 60 wherein

A is S, O or NR₂₄;
B is CR₂₃ or N;

R₂₃ is independently selected from the group consisting of hydrogen, halo, perhalo(C₁₋₁₀)alkyl, amino, thio, cyano, CF₃, nitro, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl (C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₈₋₁₂)bicycloaryl, carbonyl (C₁₋₃)alkyl,

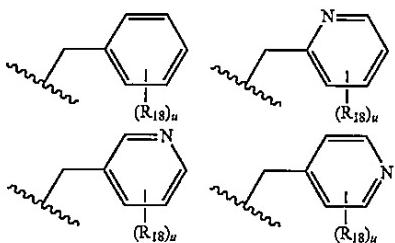
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thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and

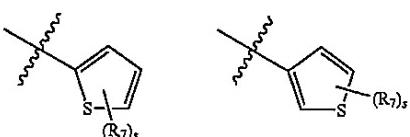
R_{24} is independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, amino, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{8-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

In another particular variation, the present invention provides compounds wherein M is CR_4 and where R_4 is selected from the group consisting of



wherein u is 0, 1, 2, 3, 4, or 5; and each R_{18} is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3 , (C_{1-10})alkyl, alkenyl, alkyanyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In yet another variation, there is provided compounds wherein M is CR_4 and where R_4 is selected from the group consisting of



wherein s is 0, 1, 2, or 3; and each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3 , (C_{1-10})alkyl, alkenyl, alkyanyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent R_5 and R_6 :

In particular variations of the present invention, there is provided compounds wherein R_5 and R_6 are hydrogen. In yet another variation, R_5 and R_6 are taken together to form a ring. In yet another variation, at least one of R_5 and R_6 is a halide, such as fluorine.

In another variation of the invention, there is provided compounds wherein at least one of R_5 and R_6 is a substituted

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or unsubstituted —(C_{1-8})alkylene R_{13} , wherein R_{13} is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{4-12})cycloalkyl, (C_{6-12})aryl, hetero(C_{5-12})aryl, (C_{9-12})bicycloalkyl, hetero(C_{9-12})bicycloalkyl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

In another particular variation of the above compounds, R_5 and R_6 are hydrogen, m is 1 or 2, and each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3 , cyano, nitro, hydroxy, alkyl, alkenyl, alkyanyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In regard to particular variations of the invention, there is provided compounds wherein two R_7 are taken together to form a substituted or unsubstituted fused or bridged ring.

In yet another particular variation, there is provided compounds wherein n is 1, 2 or 3; and R_5 and R_6 are hydrogen. In another variation, n is 1 or 2; R_3 is selected from the group consisting of amino, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, and a substituted or unsubstituted 4, 5, 6 or 7 membered ring; and R_5 and R_6 are hydrogen.

In one particular variation of the above compounds, R_5 and R_6 are hydrogen and R_7 is 2-cyano. In another variation of the above compound, n is 1. In yet another particular variation of the above compounds, n is 1, 2 or 3; R_5 and R_6 are hydrogen; and R_3 is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl (C_{1-5})alkyl, (C_{9-12})bicycloaryl, and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

According to particular variation of the above compounds, n is 1, 2 or 3; R_5 and R_6 are hydrogen; and each R_7 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, alkenyl, alkyanyl, CF_3 , cyano, nitro, hydroxy, heteroaryl, aryloxy, heteroaryloxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Substituent R_7 :

In particular variations of the above, there is provided compounds wherein two R_7 are taken together to form a substituted or unsubstituted fused ring. In another particular variation, two R_7 are taken together to form a substituted or unsubstituted bridged ring.

According to particular variations of the above compounds, two of T, U, V, W and Y are taken together and substituted through available valencies to form a substituted or unsubstituted ring fused or bridged to the ring formed by T, U, V, W and Y.

Substituent R_2 :

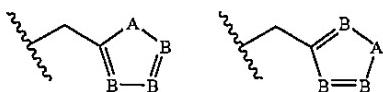
According to each of the above embodiments and variations, the present invention provides compounds wherein R_2 is a substituted or unsubstituted (C_{1-10})alkyl. In another variation, R_2 is a substituted or unsubstituted (C_{1-4})alkyl. In yet another variation, R_2 is —Y—Z wherein Y a linker providing 1, 2 or 3 atom separation between Z and the ring to which Y is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and Z is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, het-

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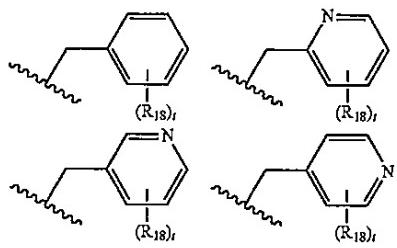
eroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

In yet another variation, R₂ is selected from the group consisting of



wherein A is S, O or NR₂₄; B is CR₂₃ or N; R₂₃ is independently selected from the group consisting of hydrogen, halo, perhalo(C₁₋₁₀)alkyl, amino, thio, cyano, CF₃, nitro, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl (C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₈₋₁₂)bicycloaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted; and R₂₄ is independently selected from the group consisting of hydrogen, perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl (C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₈₋₁₂)bicycloaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, imino group, carbonyl group, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, and sulfinyl group, each substituted or unsubstituted.

In yet another variation, R₂ is selected from the group consisting of



wherein t is 0, 1, 2, 3, 4, or 5; and each R₁₈ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, (C₁₋₁₀)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imine group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

Particular examples of DPP-IV inhibitors according to the present invention include, but are not limited to:

- 2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;
- 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;
- 2-[6-[3-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

- 55 2-[6-[3-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione];
- 2-[6-[3 (R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 50 6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-di-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-di-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- (R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)methyl)-4-fluorobenzonitrile; and
- 2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile.

- 60 Particular examples of DPP-IV inhibitors according to the present invention further include:
- 2-[6-[3 (R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3 (R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 65 2-[6-[3 (R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

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- 2-[6-[3-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;
- 5 6-[3-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;
- 6-[3-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 10 6-[3-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 6-[3-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 15 2-[6-(Azepan-3 (±)-ylamino)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (14);
- 2-[6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 20 2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 25 2-[6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-yl-methyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 30 2-[6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 35 6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;
- 40 3-[4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid methyl ester;
- 3-[4-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid;
- 45 6-[3-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione;
- 2-[6-[3 (R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 50 6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-di-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-di-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- (R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)methyl)-4-fluorobenzonitrile; and
- 2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile.

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- 2-[6-[3 (R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
- 2-[6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 2-[6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
- 6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;
- 3-[4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid methyl ester;
- 3-[4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid;
- 6-[3(R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluorobenzyl)-1H-pyrimidine-2,4-dione; and
- 2-[6-(3(R)-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile.

In another embodiment, the present invention provides the compounds in the form of a pharmaceutically acceptable salt.

In yet another embodiment, the present invention provides the compounds present in a mixture of stereoisomers. In yet another embodiment, the present invention provides the compounds as a single stereoisomer.

In yet another embodiment, the present invention provides pharmaceutical compositions comprising the compound as an active ingredient. In yet another variation, the present invention provides pharmaceutical compositions wherein the composition is a solid formulation adapted for oral administration. In yet another particular variation, the present invention provides pharmaceutical composition wherein the composition is a tablet. In another particular variation, the present invention provides the pharmaceutical composition wherein the composition is a liquid formulation adapted for oral administration. In yet another particular variation, the present invention provides pharmaceutical composition wherein the composition is a liquid formulation adapted for parenteral administration.

In yet another particular variation, the present invention provides the pharmaceutical composition comprising the

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compound of the invention wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, and intrathecally.

In another embodiment, the present invention provides a kit comprising a compound of the present invention and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the compound is to be administered, storage information for the compound, dosing information and instructions regarding how to administer the compound. In another embodiment, the present invention provides the kit that comprises the compound in a multiple dose form.

In another embodiment, the present invention provides an article of manufacture comprising a compound of the present invention, and packaging materials. In another variation, the packaging material comprises a container for housing the compound. In yet another variation, the invention provides the article of manufacture wherein the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition.

In another variation, the present invention provides the article of manufacture wherein the article of manufacture comprises the compound in a multiple dose form.

In another embodiment, the present invention provides a method of inhibiting DPP-IV comprising contacting DPP-IV with a compound according to the present invention.

In another embodiment, the present invention provides a method of inhibiting DPP-IV comprising causing a compound according to the present invention to be present in a subject in order to inhibit DPP-IV in vivo.

In another embodiment, the present invention provides a method of inhibiting DPP-IV comprising: administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits DPP-IV in vivo, the second compound being a compound of the present invention.

In another embodiment, the present invention provides therapeutic method comprising: administering a compound according to the present invention to a subject.

In another embodiment, the present invention provides a method of treating a disease state for which DPP-IV possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising causing a compound of the present invention to be present in a subject in a therapeutically effective amount for the disease state.

In another embodiment, the present invention provides a method of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

In another embodiment, the present invention provides a method of treating a disease where the disease is type I or type II diabetes.

In another embodiment, the present invention provides a method of treating autoimmune disorders such as, but not limited to, rheumatoid arthritis, psoriasis, and multiple sclerosis in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

In yet another embodiment, the present invention provides a method of treating cancer where the cancer treated is colorectal, prostate, breast, thyroid, skin, lung, or head and neck.

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In another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hematopoietic cell activation or concentration in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

In another embodiment, the present invention provides a method of treating HIV infection in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

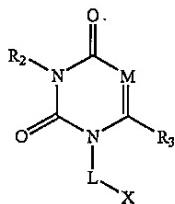
In yet another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hematopoietic cell activation or concentration in a patient in need thereof, wherein the condition is a side effect of chemotherapy or radiation therapy.

In yet another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hematopoietic cell activation or concentration in a patient in need thereof, wherein the condition is a result of kidney failure.

In yet another embodiment, the present invention provides a method of treating a condition characterized by inadequate lymphocyte or hematopoietic cell activation or concentration in a patient in need thereof, wherein the condition is a result of a bone marrow disorder.

In another embodiment, the present invention provides a method of treating a condition characterized by immunodeficiency symptoms in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to the present invention.

In yet another embodiment, the present invention provides a process for producing a pyrimidin-dione of the formula:



wherein

M is N or CR4;

R2 is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfanyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

R3 is selected from the group consisting of perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfanyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and a substituted or unsubstituted 3, 4, 5, 6 or 7 membered ring;

R4 is hydrogen or is selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl,

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sulfonyl(C₁₋₃)alkyl, sulfanyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

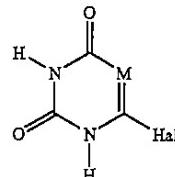
L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfanyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

the process comprising the steps of:

(i) contacting a compound of the formula A

A



wherein Hal is halogen;
with a compound of the formula B

X-L-LG

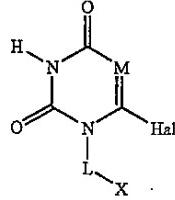
B

wherein LG is a leaving group;

L is a linker providing 1, 2 or 3 atom separation between X and the ring to which L is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

X is selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl(C₁₋₃)alkyl, thiocarbonyl(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, sulfanyl(C₁₋₃)alkyl, imino(C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; under conditions sufficient to produce a compound of the formula C

C



(ii) contacting the compound of formula C with a compound of formula D

R2-LG'

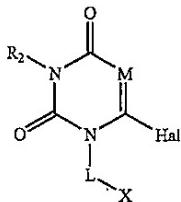
D

wherein LG' is a leaving group;

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under conditions sufficient to produce a compound of the formula E;



wherein R₂ is selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl (C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl (C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl (C₁₋₃)alkyl, imino (C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted; and

(iii) contacting the compound of formula E with a compound of formula R₃-H under conditions sufficient to produce the pyrimidin-dione.

In one variation the pyrimidin-dione product is further converted to an acid addition salt. In particular variations, the acid addition salt is selected from the group consisting of acetate, citrate, hydrochloride, L-lactate, succinate, sulfate, p-toluenesulfonate, benzenesulfonate, benzoate, methanesulfonate, naphthylene-2-sulfonate, propionate, p-toluene sulfonate, hydrobromate, hydroiodate, R-mandelate, and L-tartarate.

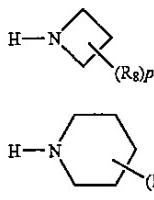
In another variation of each of the above embodiments and variations, Hal is selected from the group consisting of Br, Cl and F in the compound of formula A.

In yet another variation of each of the above embodiments and variations, the leaving group LG is selected from the group consisting of Br, Cl and I.

In a further variation of each of the above embodiments and variations, step (ii) further comprises the addition of a base. In particular variations, the base is potassium carbonate.

In still another variation of each of the above embodiments and variations, product E is further purified before subjecting it to step (iii). In a particular variation, the purification of product E is performed by solvent washes and/or by chromatography.

In another variation of each of the above embodiments and variations, R₃-H is a secondary amine or an amine hydrochloride. In a particular variation, R₃-H is selected from the group consisting of



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wherein p is 0-12 and each R₈ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, or the mono- or di-hydrochloride salt.

In yet another variation of each of the above embodiments and variations, step iii) further comprises purifying the product by washing the product with one or more organic solvents or mixtures of solvents and/or by column chromatography.

In a further variation of each of the above embodiments and variations, L is selected from the group consisting of -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -C(O)-, -CH₂C(O)-, -C(O)CH₂-, -CH₂-C(O)CH₂-, -C(O)CH₂CH₂-, -CH₂CH₂C(O)-, -O-, -OCH₂-, -CH₂O-, -CH₂OCH₂-, -OCH₂CH₂-, -CH₂CH₂O-, -N(CH₃)-, -NHCH₂-, -CH₂NH-, -CH₂NHCH₂-, -NHCH₂CH₂-, -CH₂CH₂NH-, -NH-C(O)-, -NCH₃-C(O)-, -C(O)NH-, -C(O)NCH₃-, -NHC(O)CH₂-, -C(O)NHCH₂-, -C(O)CH₂NH-, -CH₂NHC(O)-, -CH₂C(O)NH-, -NHCH₂C(O)-, -S-, -SCH₂-, -CH₂S-, -SCH₂CH₂-, -CH₂SCH₂-, -CH₂CH₂S-, -C(O)S-, -C(O)SCH₂-, -CH₂C(O)S-, -C(O)CH₂S-, and -CH₂SC(O)-, each substituted or unsubstituted. In a particular variation, L is selected from the group consisting of

-CH₂-, -C(O)-, -CH₂C(O)-, -C(O)CH₂-, -CH₂-C(O)CH₂-, -C(O)CH₂CH₂-, and -CH₂CH₂C(O)-, each substituted or unsubstituted.

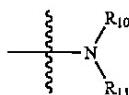
In still another variation of each of the above embodiments and variations, -L-X taken together is selected from the group consisting of -(CH₂)-(2-cyano)phenyl; -(CH₂)-(3-cyano)phenyl; -(CH₂)-(2-hydroxy)phenyl; -(CH₂)-(3-hydroxy)phenyl; -(CH₂)-(2-alkenyl)phenyl; -(CH₂)-(3-alkenyl)phenyl; -(CH₂)-(2-alkynyl)phenyl; -(CH₂)-(3-alkynyl)phenyl; -(CH₂)-(2-methoxy)phenyl; -(CH₂)-(3-methoxy)phenyl; -(CH₂)-(2-nitro)phenyl; -(CH₂)-(3-nitro)phenyl; -(CH₂)-(2-carboxy)phenyl; -(CH₂)-(3-carboxy)phenyl; -(CH₂)-(2-carboxamido)phenyl; -(CH₂)-(3-carboxamido)phenyl; -(CH₂)-(2-sulfonamido)phenyl; -(CH₂)-(3-sulfonamido)phenyl; -(CH₂)-(2-tetrazolyl)phenyl; -(CH₂)-(3-tetrazolyl)phenyl; -(CH₂)-(2-aminomethyl)phenyl; -(CH₂)-(3-aminomethyl)phenyl; -(CH₂)-(2-hydroxymethyl)phenyl; -(CH₂)-(3-hydroxymethyl)phenyl; -(CH₂)-(2-phenyl)phenyl; -(CH₂)-(3-phenyl)phenyl; -(CH₂)-(2-halo)phenyl; -(CH₂)-(3-halo)phenyl; -(CH₂)-(2-CONH₂)phenyl; -(CH₂)-(3-CONH₂)phenyl; -(CH₂)-(2-CONH(C₁₋₇)alkyl)phenyl; -(CH₂)-(3-CONH(C₁₋₇)alkyl)phenyl; -(CH₂)-(2-CO₂(C₁₋₇)alkyl)phenyl; -(CH₂)-(3-CO₂(C₁₋₇)alkyl)phenyl; -(CH₂)-(2-NH₂)phenyl; -(CH₂)-(3-NH₂)phenyl; -(CH₂)-(2-(C₃₋₇)alkyl)phenyl; -(CH₂)-(3-(C₃₋₇)alkyl)phenyl; -(CH₂)-(2-(C₃₋₇)cycloalkyl)phenyl; -(CH₂)-(3-(C₃₋₇)cycloalkyl)phenyl; -(CH₂)-(2-aryl)phenyl; -(CH₂)-(3-aryl)phenyl; -(CH₂)-(2-heteroaryl)phenyl; -(CH₂)-(3-heteroaryl)phenyl; -(CH₂)-(2-bromo-5-fluoro phenyl); -(CH₂)-(2-chloro-5-fluoro phenyl); -(CH₂)-(2-cyano-5-fluoro phenyl); -(CH₂)-(2,5-dichloro phenyl); -(CH₂)-(2,5-difluoro phenyl); -(CH₂)-(2,5-dibromo phenyl); -(CH₂)-(2-bromo-3,5-difluoro phenyl); -(CH₂)-(2,3,5-trifluoro phenyl); -(CH₂)-(2,3,5,6-tetrafluorophenyl); -(CH₂)-(2-bromo-3,5,6-trifluoro phenyl); -(CH₂)-(2-chloro-3,5,6-trifluoro phenyl); -(CH₂)-(2-cyano-3,5,6-difluoro phenyl); -(CH₂)-(2-cyano-3,5,6-trifluoro phenyl);

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nyl; —(CH₂)-(2-heterocycloalkyl)phenyl; and —(CH₂)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

In a further variation of each of the above embodiments and variations, M is CH, and R₃ comprises the formula

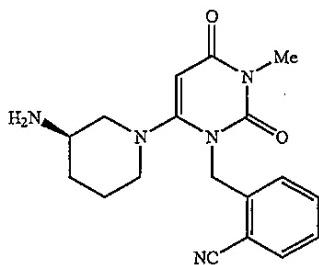


wherein R₁₀ and R₁₁ are each independently selected from the group consisting of hydrogen, perhalo(C₁₋₁₀)alkyl, amino, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl (C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, and sulfinyl group, each substituted or unsubstituted, or R₁₀ and R₁₁ are taken together to form a 4, 5, 6, or 7 membered ring, each substituted or unsubstituted.

In yet a further variation, M is CH and R₃ is selected from the group consisting of 3-amino-piperidinyl-1-yl, 3-aminoethyl-pyrrolidin-1-yl, 2-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminocyclopent-1-yl, 3-aminomethylcyclopent-1-yl, 3-aminomethylcyclohex-1-yl, 3-aminohexahydroazepin-1-yl, 3-amino-cyclohex-1-yl, piperazin-1-yl, homopiperazin-1-yl, 3-amino-pyrrolidin-1-yl, R-3-aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, 3-amino-cyclohex-1-yl, 3-amino-cyclopent-1-yl, and 3-amino-pyrrolidin-1-yl, each substituted or unsubstituted.

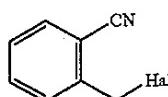
In still a further variation, M is CH and R₂ is a substituted or unsubstituted (C₁₋₁₀)alkyl.

In another of its embodiments, the present invention provides a process for producing a pyrimidin-dione of the formula



comprising:

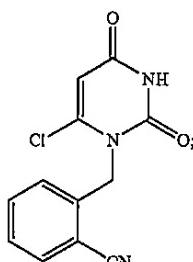
(i) admixing 6-chloro-1H-pyrimidine-2,4-dione with an aryl halide of the formula



where Hal is Br, Cl, or I, under conditions sufficient to produce a compound of the formula

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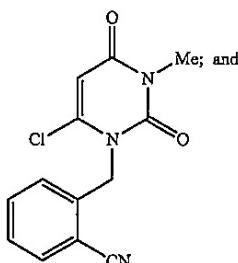
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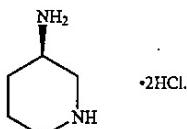
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(ii) alkylating the above product with a methyl halide under conditions sufficient to form a compound of the formula



(iii) condensing the above product with a compound of the formula



In one variation of the above embodiment, the process for producing a pyrimidin-dione further comprises the formation of an acid addition salt. In one particular variation, the acid addition salt is a benzoate salt.

In another variation of each of the above embodiments and variations, the pyrimidin-dione is selected from the group consisting of:

2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile;

2-[6-[3-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-[6-[3-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-[6-[3-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

2-[6-[3-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione;

6-[3-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

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- 6-[3-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 6-[3-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 6-[3-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 2-[6-{Azepan-3(±)-ylamino}-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (14);
 2-[6-{3(±)-Amino-azepan-1-yl}-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3-Amino-piperidin-1-yl}-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3-Amino-piperidin-1-yl}-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3-Amino-piperidin-1-yl}-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3-Amino-piperidin-1-yl}-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3-Amino-piperidin-1-yl}-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 6-[3-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;
 3-[4-{3-Amino-piperidin-1-yl}-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid methyl ester;
 3-[4-{3-Amino-piperidin-1-yl}-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid;
 2-[6-{3(R)-Amino-piperidin-1-yl}-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-di-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-di-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 (R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)methyl)-4-fluorobenzonitrile; and
 6-[3-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione.

The process of Claim 133, wherein the pyrimidin-dione is selected from the group consisting of:
 2-[6-{3(R)-Amino-piperidin-1-yl}-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-1-benzonitrile;
 2-[6-{3(R)-Amino-piperidin-1-yl}-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3(R)-Amino-piperidin-1-yl}-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3(R)-Amino-piperidin-1-yl}-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;

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- 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione;
 2-[6-{3(R)-Amino-piperidin-1-yl}-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3(R)-Amino-piperidin-1-yl}-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3(R)-Amino-piperidin-1-yl}-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3(R)-Amino-piperidin-1-yl}-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 2-[6-{3(R)-Amino-piperidin-1-yl}-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile;
 6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile;
 3-[4-{3(R)-Amino-piperidin-1-yl}-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid methyl ester;
 3-[4-{3(R)-Amino-piperidin-1-yl}-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid; and
 6-[3 (R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione.

In still another variation of each of the above embodiments and variations, the pyrimidin-dione is present as a mixture of stereoisomers. In yet another variation, the pyrimidin-dione comprises a single stereoisomer.

It is noted in regard to all of the embodiments, and any further embodiments, variations, or individual compounds described or claimed herein that all such embodiments, variations, and/or individual compounds are intended to encompass all pharmaceutical acceptable salt forms whether in the form of a single stereoisomer or mixture of stereoisomers unless it is specifically specified otherwise. Similarly, when one or more potentially chiral centers are present in any of the embodiments, variations, and/or individual compounds specified or claimed herein, both possible chiral centers are intended to be encompassed unless it is specifically specified otherwise.

A. Salts, Hydrates, and Prodrugs of DPP-IV Inhibitors

It should be recognized that the compounds of the present invention may be present and optionally administered in the form of salts, hydrates and prodrugs that are converted in vivo into the compounds of the present invention. For example, it is within the scope of the present invention to convert the compounds of the present invention into and use them in the form of their pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures well known in the art.

When the compounds of the present invention possess a free base form, the compounds can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, e.g., hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, etc.; and alkyl and monoarylsulfonates such as ethanesulfonate, toluenesulfonate and benzenesulfonate; and other organic acids and their corresponding salts such as

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acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate and ascorbate. Further acid addition salts of the present invention include, but are not limited to: adipate, alginate, arginate, aspartate, bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptaoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, iso-butylate, lactate, lactobionate, malate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate and phthalate. It should be recognized that the free base forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base forms for the purposes of the present invention.

When the compounds of the present invention possess a free acid form, a pharmaceutically acceptable base addition salt can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Examples of such bases are alkali metal hydroxides including potassium, sodium and lithium hydroxides; alkaline earth metal hydroxides such as barium and calcium hydroxides; alkali metal alkoxides, e.g. potassium ethanolate and sodium propanolate; and various organic bases such as ammonium hydroxide, piperidine, diethanolamine and N-methylglutamine. Also included are the aluminum salts of the compounds of the present invention. Further base salts of the present invention include, but are not limited to: copper, ferric, ferrous, lithium, magnesium, manganic, manganese, potassium, sodium and zinc salts. Organic base salts include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, e.g., arginine, betaine, caffeine, chloroprocaine, choline, N,N-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, iso-propylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)-methylamine (tromethamine). It should be recognized that the free acid forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid forms for the purposes of the present invention.

Compounds of the present invention that comprise basic nitrogen-containing groups may be quaternized with such agents as (C₁₋₄)alkyl halides, e.g., methyl, ethyl, iso-propyl and tert-butyl chlorides, bromides and iodides; di(C₁₋₄)alkyl sulfates, e.g., dimethyl, diethyl and diethyl sulfates; (C₁₀₋₁₈)alkyl halides, e.g., decyl, dodecyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aryl (C₁₋₄)alkyl halides, e.g., benzyl chloride and phenethyl bromide. Such salts permit the preparation of both water-soluble and oil-soluble compounds of the present invention.

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N-oxides of compounds according to the present invention can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0° C. Alternatively, the N-oxides of the compounds can be prepared from the N-oxide of an appropriate starting material.

Prodrug derivatives of compounds according to the present invention can be prepared by modifying substituents of compounds of the present invention that are then converted in vivo to a different substituent. It is noted that in many instances, the prodrugs themselves also fall within the scope of the range of compounds according to the present invention. For example, prodrugs can be prepared by reacting a compound with a carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, para-nitrophenyl carbonate, or the like) or an acylating agent. Further examples of methods of making prodrugs are described in Saulnier et al. (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985.

Protected derivatives of compounds of the present invention can also be made. Examples of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Compounds of the present invention may also be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

A "pharmaceutically acceptable salt", as used herein, is intended to encompass any compound according to the present invention that is utilized in the form of a salt thereof, especially where the salt confers on the compound improved pharmacokinetic properties as compared to the free form of compound or a different salt form of the compound. The pharmaceutically acceptable salt form may also initially confer desirable pharmacokinetic properties on the compound that it did not previously possess, and may even positively affect the pharmacodynamics of the compound with respect to its therapeutic activity in the body. An example of a pharmacokinetic property that may be favorably affected is the manner in which the compound is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation and excretion of the compound. While the route of administration of the pharmaceutical composition is important, and various anatomical, physiological and pathological factors can critically affect bioavailability, the solubility of the compound is usually dependent upon the character of the particular salt form thereof, which it utilized. One of skill in the art will appreciate that an aqueous solution of the compound will provide the most rapid absorption of the compound into the body of a subject being treated, while lipid solutions and suspensions, as well as solid dosage forms, will result in less rapid adsorption of the compound.

3. Indications for Use of DPP-IV Inhibitors

DPP-IV is believed to contribute to the pathology and/or symptomology of several different diseases such that reduction of the activity of DPP-IV in a subject through inhibition may be used to therapeutically address these disease states. Examples of various diseases that may be treated using the

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DPP-IV inhibitors of the present invention are described herein. It is noted that additional diseases beyond those disclosed herein may be later identified as the biological roles that DPP-IV plays in various pathways becomes more fully understood.

One set of indications that DPP-IV inhibitors of the present invention may be used to treat are those involving the prevention and treatment of diabetes and obesity, in particular type 2 diabetes mellitus, diabetic dyslipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation and obesity.

DPP-IV inhibitors of the present invention may also be used as immunosuppressants (or cytokine release suppressant drugs) for the treatment of among other things: organ transplant rejection; autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis; and the treatment of AIDS.

DPP-IV inhibitors of the present invention may also be used for treating various cancers including breast cancer, lung cancer and prostate cancer.

DPP-IV inhibitors of the present invention may also be used to treat dermatological diseases such as psoriasis, rheumatoid arthritis (RA) and lichen planus.

DPP-IV inhibitors of the present invention may also be used to treat infertility and amenorrhea.

DPP-IV inhibitors of the present invention may also be used to modulate cleavage of various cytokines (stimulating hematopoietic cells), growth factors and neuropeptides. For example, such conditions occur frequently in patients who are immunosuppressed, for example, as a consequence of chemotherapy and/or radiation therapy for cancer.

DPP-IV inhibitors of the present invention may also be used prevent or reduce cleavage of N-terminal Tyr-Ala from growth hormone-releasing factor. Accordingly, these inhibitors may be used in the treatment of short stature due to growth hormone deficiency (Dwarfism) and for promoting GH-dependent tissue growth or re-growth.

DPP-IV inhibitors of the present invention may also be used to address disease states associated with cleavage of neuropeptides and thus may be useful for the regulation or normalization of neurological disorders.

For oncology indications, DPP-IV inhibitors of the present invention may be used in conjunction with other agents to inhibit undesirable and uncontrolled cell proliferation. Examples of other anti-cell proliferation agents that may be used in conjunction with the DPP-IV inhibitors of the present invention include, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, ANGIOSTATIN™ protein, ENDOSTATIN™ protein, suramin, squalamine, tissue inhibitor of metalloproteinase-1, tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, cartilage-derived inhibitor, paclitaxel, platelet factor 4, protamine sulfate (clupeine), sulfated chitin derivatives (prepared from queen crab shells), sulfated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism, including for example, proline analogs ((1-azetidine-2-carboxylic acid (LACA)), cishydroxyproline, d,l-3,4-dehydroproline, thiaaproline, beta.-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2-(3H)-oxazolone, methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chimp-3, chymostatin, beta.-cyclodextrin tetradecasulfate, eponemycin; fumagillin, gold sodium thiomolate, d-penicillamine (CDPT), beta.-1-anticoagulase-serum, alpha.-2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide;

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angostatic steroid, carboxyaminoimidazole; metalloproteinase inhibitors such as BB94. Other anti-angiogenesis agents that may be used include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: bFGF, aFGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF and Ang-1/Ang-2. Ferrara N. and Alitalo, K. "Clinical application of angiogenic growth factors and their inhibitors" (1999) Nature Medicine 5:1359-1364.

4. Compositions Comprising DPP-IV Inhibitors

A wide variety of compositions and administration methods may be used in conjunction with the DPP-IV inhibitors of the present invention. Such compositions may include, in addition to the DPP-IV inhibitors of the present invention, conventional pharmaceutical excipients, and other conventional, pharmaceutically inactive agents. Additionally, the compositions may include active agents in addition to the DPP-IV inhibitors of the present invention. These additional active agents may include additional compounds according to the invention, and/or one or more other pharmaceutically active agents.

The compositions may be in gaseous, liquid, semi-liquid or solid form, formulated in a manner suitable for the route of administration to be used. For oral administration, capsules and tablets are typically used. For parenteral administration, reconstitution of a lyophilized powder, prepared as described herein, is typically used.

Compositions comprising DPP-IV inhibitors of the present invention may be administered or coadministered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, or intrathecally. The compounds and/or compositions according to the invention may also be administered or coadministered in slow release dosage forms.

The DPP-IV inhibitors and compositions comprising them may be administered or coadministered in any conventional dosage form. Co-administration in the context of this invention is intended to mean the administration of more than one therapeutic agent, one of which includes a DPP-IV inhibitor, in the course of a coordinated treatment to achieve an improved clinical outcome. Such co-administration may also be coextensive, that is, occurring during overlapping periods of time.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application may optionally include one or more of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; agents for the adjustment of tonicity such as sodium chloride or dextrose, and agents for adjusting the acidity or alkalinity of the composition, such as alkaline or acidifying agents or buffers like carbonates, bicarbonates, phosphates, hydrochloric acid, and organic acids like acetic and citric acid. Parenteral preparations may optionally be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

When DPP-IV inhibitors according to the present invention exhibit insufficient solubility, methods for solubilizing the compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to,

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using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

Upon mixing or adding DPP-IV inhibitors according to the present invention to a composition, a solution, suspension, emulsion or the like may be formed. The form of the resulting composition will depend upon a number of factors, including the intended mode of administration, and the solubility of the compound in the selected carrier or vehicle. The effective concentration needed to ameliorate the disease being treated may be empirically determined.

Compositions according to the present invention are optionally provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, dry powders for inhalers, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds, particularly the pharmaceutically acceptable salts, preferably the sodium salts, thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms, as used herein, refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes individually packaged tablet or capsule. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pint or gallons. Hence, multiple dose form is a multiple of unit-doses that are not segregated in packaging.

In addition to one or more DPP-IV inhibitors according to the present invention, the composition may comprise: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polyvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known in the art, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a

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sufficient quantity of a DPP-IV inhibitor of the present invention to reduce DPP-IV activity in vivo, thereby treating the disease state of the subject.

Dosage forms or compositions may optionally comprise one or more DPP-IV inhibitors according to the present invention in the range of 0.005% to 100% (weight/weight) with the balance comprising additional substances such as those described herein. For oral administration, a pharmaceutically acceptable composition may optionally comprise any one or more commonly employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate, sodium saccharin, talcum. Such compositions include solutions, suspensions, tablets, capsules, powders, dry powders for inhalers and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparing these formulations are known to those skilled in the art. The compositions may optionally contain 0.01%-100% (weight/weight) of one or more DPP-IV inhibitors, optionally 0.1-95%, and optionally 1-95%.

Salts, preferably sodium salts, of the DPP-IV inhibitors may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The formulations may further include other active compounds to obtain desired combinations of properties.

A. Formulations for Oral Administration

Oral pharmaceutical dosage forms may be as a solid, gel or liquid. Examples of solid dosage forms include, but are not limited to tablets, capsules, granules, and bulk powders. More specific examples of oral tablets include compressed, chewable lozenges and tablets that may be enteric-coated, sugar-coated or film-coated. Examples of capsules include hard or soft gelatin capsules. Granules and powders may be provided in non-effervescent or effervescent forms. Each may be combined with other ingredients known to those skilled in the art.

In certain embodiments, DPP-IV inhibitors according to the present invention are provided as solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like may optionally contain one or more of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders that may be used include, but are not limited to, microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste.

Examples of lubricants that may be used include, but are not limited to, talc, starch, magnesium or calcium stearate, lycopodium and stearic acid.

Examples of diluents that may be used include, but are not limited to, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate.

Examples of glidants that may be used include, but are not limited to, colloidal silicon dioxide.

Examples of disintegrating agents that may be used include, but are not limited to, crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose.

Examples of coloring agents that may be used include, but are not limited to, any of the approved certified water soluble

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FD and C dyes, mixtures thereof, and water insoluble FD and C dyes suspended on alumina hydrate.

Examples of sweetening agents that may be used include, but are not limited to, sucrose, lactose, mannitol and artificial sweetening agents such as sodium cyclamate and saccharin, and any number of spray-dried flavors.

Examples of flavoring agents that may be used include, but are not limited to, natural flavors extracted from plants such as fruits and synthetic blends of compounds that produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate.

Examples of wetting agents that may be used include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether.

Examples of anti-emetic coatings that may be used include, but are not limited to, fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates.

Examples of film coatings that may be used include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

If oral administration is desired, the salt of the compound may optionally be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it may optionally additionally comprise a liquid carrier such as a fatty oil. In addition, dosage unit forms may optionally additionally comprise various other materials that modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents.

Compounds according to the present invention may also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may optionally comprise, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The DPP-IV inhibitors of the present invention may also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antacids, H₂ blockers, and diuretics. For example, if a compound is used for treating asthma or hypertension, it may be used with other bronchodilators and anti-hypertensive agents, respectively.

Examples of pharmaceutically acceptable carriers that may be included in tablets comprising DPP-IV inhibitors of the present invention include, but are not limited to binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets may be compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets may be compressed tablets that have been coated with polymers or other suitable coating. Multiple compressed tablets may be compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in tablets. Flavoring and sweetening agents may be used in tablets, and are especially useful in the formation of chewable tablets and lozenges.

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Examples of liquid oral dosage forms that may be used include, but are not limited to, aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules.

Examples of aqueous solutions that may be used include, but are not limited to, elixirs and syrups. As used herein, elixirs refer to clear, sweetened, hydroalcoholic preparations. Examples of pharmaceutically acceptable carriers that may be used in elixirs include, but are not limited to solvents. Particular examples of solvents that may be used include glycerin, sorbitol, ethyl alcohol and syrup. As used herein, syrups refer to concentrated aqueous solutions of a sugar, for example, sucrose. Syrups may optionally further comprise a preservative.

Emulsions refer to two-phase systems in which one liquid is dispersed in the form of small globules throughout another liquid. Emulsions may optionally be oil-in-water or water-in-oil emulsions. Examples of pharmaceutically acceptable carriers that may be used in emulsions include, but are not limited to non-aqueous liquids, emulsifying agents and preservatives.

Examples of pharmaceutically acceptable substances that may be used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents.

Examples of pharmaceutically acceptable substances that may be used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide.

Coloring and flavoring agents may optionally be used in all of the above dosage forms.

Particular examples of preservatives that may be used include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol.

Particular examples of non-aqueous liquids that may be used in emulsions include mineral oil and cottonseed oil.

Particular examples of emulsifying agents that may be used include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate.

Particular examples of suspending agents that may be used include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as sodium cyclamate and saccharin.

Particular examples of wetting agents that may be used include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether.

Particular examples of organic acids that may be used include citric and tartaric acid.

Sources of carbon dioxide that may be used in effervescent compositions include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof.

Particular examples of flavoring agents that may be used include natural flavors extracted from plants such fruits, and synthetic blends of compounds that produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., for example, in a polyethylene glycol, may be diluted with a sufficient quantity

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of a pharmaceutically acceptable liquid carrier, e.g. water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g. propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Pat. Nos. Re 28,819 and 4,358,603.

B. Injectables, Solutions and Emulsions

The present invention is also directed to compositions designed to administer the DPP-IV inhibitors of the present invention by parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables may be prepared in any conventional form, for example as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions.

Examples of excipients that may be used in conjunction with injectables according to the present invention include, but are not limited to water, saline, dextrose, glycerol or ethanol. The injectable compositions may also optionally comprise minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, e.g., U.S. Pat. No. 3,710,795) is also contemplated herein. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the formulations includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as the lyophilized powders described herein, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

When administered intravenously, examples of suitable carriers include, but are not limited to physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Examples of pharmaceutically acceptable carriers that may optionally be used in parenteral preparations include, but are not limited to aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles that may optionally be used include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection.

Examples of nonaqueous parenteral vehicles that may optionally be used include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil.

Antimicrobial agents in bacteriostatic or fungistatic concentrations may be added to parenteral preparations, particularly when the preparations are packaged in multiple-dose containers and thus designed to be stored and multiple ali-

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quots to be removed. Examples of antimicrobial agents that may used include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride.

Examples of isotonic agents that may be used include sodium chloride and dextrose. Examples of buffers that may be used include phosphate and citrate. Examples of antioxidants that may be used include sodium bisulfite. Examples of local anesthetics that may be used include procaine hydrochloride. Examples of suspending and dispersing agents that may be used include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Examples of emulsifying agents that may be used include Polysorbate 80 (TWEEN 80). A sequestering or chelating agent of metal ions include EDTA.

Pharmaceutical carriers may also optionally include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of a DPP-IV inhibitor in the parenteral formulation may be adjusted so that an injection administers a pharmaceutically effective amount sufficient to produce the desired pharmacological effect. The exact concentration of a DPP-IV inhibitor and/or dosage to be used will ultimately depend on the age, weight and condition of the patient or animal as is known in the art.

Unit-dose parenteral preparations may be packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration should be sterile, as is known and practiced in the art.

Injectables may be designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the DPP-IV inhibitor to the treated tissue(s). The DPP-IV inhibitor may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment will be a function of the location of where the composition is parenterally administered, the carrier and other variables that may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens may need to be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations. Hence, the concentration ranges set forth herein are intended to be exemplary and are not intended to limit the scope or practice of the claimed formulations.

The DPP-IV inhibitor may optionally be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease state and may be empirically determined.

C. Lyophilized Powders

The DPP-IV inhibitors of the present invention may also be prepared as lyophilized powders, which can be reconstituted

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for administration as solutions, emulsions and other mixtures. The lyophilized powders may also be formulated as solids or gels.

Sterile, lyophilized powder may be prepared by dissolving the compound in a sodium phosphate buffer solution containing dextrose or other suitable excipient. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Briefly, the lyophilized powder may optionally be prepared by dissolving dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent, about 1-20%, preferably about 5 to 15%, in a suitable buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Then, a DPP-IV inhibitor is added to the resulting mixture, preferably above room temperature, more preferably at about 30-35° C., and stirred until it dissolves. The resulting mixture is diluted by adding more buffer to a desired concentration. The resulting mixture is sterile filtered or treated to remove particulates and to insure sterility, and apportioned into vials for lyophilization. Each vial may contain a single dosage or multiple dosages of the DPP-IV inhibitor.

D. Topical Administration

The DPP-IV inhibitors of the present invention may also be administered as topical mixtures. Topical mixtures may be used for local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The DPP-IV inhibitors may be formulated as aerosols for topical application, such as by inhalation (see, U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

The DPP-IV inhibitors may also be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the DPP-IV inhibitor alone or in combination with other pharmaceutically acceptable excipients can also be administered.

E. Formulations for Other Routes of Administration

Depending upon the disease state being treated, other routes of administration, such as topical application, transdermal patches, and rectal administration, may also be used. For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum that melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin,

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carbowax, (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax.

Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm. Tablets and capsules for rectal administration may be manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

F. Examples of Formulations

The following are particular examples of oral, intravenous and tablet formulations that may optionally be used with compounds of the present invention. It is noted that these formulations may be varied depending on the particular compound being used and the indication for which the formulation is going to be used.

ORAL FORMULATION

Compound of the Present Invention	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

Compound of the Present Invention	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of the Present Invention	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

5. Kits Comprising DPP-IV Inhibitors

The invention is also directed to kits and other articles of manufacture for treating diseases associated with DPP-IV. It is noted that diseases are intended to cover all conditions for which the DPP-IV possesses activity that contributes to the pathology and/or symptomology of the condition.

In one embodiment, a kit is provided that comprises a composition comprising at least one DPP-IV inhibitor of the present invention in combination with instructions. The instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one DPP-IV inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally comprise additional components, such as syringes

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for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

It is noted that the packaging material used in kits and articles of manufacture according to the present invention may form a plurality of divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container that is employed will depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle that is in turn contained within a box. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral, topical, transdermal and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

One particular example of a kit according to the present invention is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter that indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

EXAMPLES

1. Preparation Of DPP-IV Inhibitors

Various methods may be developed for synthesizing compounds according to the present invention. Representative methods for synthesizing these compounds are provided in

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the Examples. It is noted, however, that the compounds of the present invention may also be synthesized by other synthetic routes that others may devise.

It will be readily recognized that certain compounds according to the present invention have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (e.g., chiral centers). It is recognized that synthesis of compounds according to the present invention may result in the creation of mixtures of different stereoisomers (enantiomers, diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

Various methods for separating mixtures of different stereoisomers are known in the art. For example, a racemic mixture of a compound may be reacted with an optically active resolving agent to form a pair of diastereoisomeric compounds. The diastereomers may then be separated in order to recover the optically pure enantiomers. Dissociable complexes may also be used to resolve enantiomers (e.g., crystalline diastereoisomeric salts). Diastereomers typically have sufficiently distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) that they can be readily separated by taking advantage of these dissimilarities. For example, diastereomers can typically be separated by chromatography or by separation/resolution techniques based upon differences in solubility. A more detailed description of techniques that can be used to resolve stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

Compounds according to the present invention can also be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

The N-oxides of compounds according to the present invention can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0° C. Alternatively, the N-oxides of the compounds can be prepared from the N-oxide of an appropriate starting material.

Compounds in an unoxidized form can be prepared from N-oxides of compounds by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium

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borylhydride, sodium borylhydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80° C.

Prodrug derivatives of the compounds can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al. (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds can be made by methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Compounds according to the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds according to the present invention can also be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
μL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
i.v. (intravenous);	Hz (Hertz);
MHz (megahertz);	mol (moles);
mmol (millimoles);	RT (ambient temperature);
min (minutes); h (hours);	TLC (thin layer chromatography);
mp (melting point);	RP (reverse phase);
Tr (retention time);	

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-continued

MeOH (methanol);	i-PrOH (isopropanol);
TEA (triethylamine);	TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride);	THF (tetrahydrofuran);
DMSO (dimethylsulfoxide);	EtOAc (ethyl acetate);
DME (1,2-dimethoxyethane);	DCM (dichloromethane);
DCE (dichloroethane);	DMF (N,N-dimethylformamide);
DMPU (N,N'-dimethylpropyleneurea);	CDI (1,1-carbonyldiimidazole);
IBCF (isobutyl chloroformate);	HOAc (acetic acid);
HOSu (N-hydroxysuccinimido);	HOBT (1-hydroxybenzotriazole);
Et ₂ O (diethyl ether);	EDCI (ethylcarbodiimino hydrochloride);
BOC (tert-butyloxycarbonyl);	FMOC (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimino);	CBZ (benzyloxycarbonyl);
Ac (acetyl);	atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl);	TMS (trimethylsilyl);
TIPS (triisopropylsilyl);	TBS (t-butyl(dimethylsilyl));
DMAP (4-(dimethylaminopyridine);	Me (methyl);
OMe (methoxy);	Et (ethyl);
Et (ethyl);	tBu (tert-butyl);
HPLC (high pressure liquid chromatography);	
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);	
TBAF (tetra-n-butylammonium fluoride);	
mCPBA (meta-chloroperbenzoic acid).	

25 All references to ether or Et₂O are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C. (degrees Centigrade). All reactions conducted under an inert atmosphere at RT unless otherwise noted.

30 ¹H NMR spectra were recorded on a Bruker Avance 400. Chemical shifts are expressed in parts per million (ppm). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

35 Low-resolution mass spectra (MS) and compound purity data were acquired on a Waters ZQ LC/MS single quadrupole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light scattering detector (ELSD). Thin-layer chromatography was performed on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, Ninhydrin or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

45 2. Synthetic Schemes for DPP-IV Inhibitors of the Present Invention

50 DPP-IV inhibitors according to the present invention may be synthesized according to a variety of reaction schemes. Some illustrative schemes are provided herein in the examples. Other reaction schemes could be readily devised by those skilled in the art.

55 In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T. W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

60 By varying the Q¹ and Q², R₁, R₂, and R₃ groups, a wide variety of different DPP-IV inhibitors according to the present invention may be synthesized.

65 In each of the above reaction schemes, the various substituents may be selected from among the various substituents otherwise taught herein.

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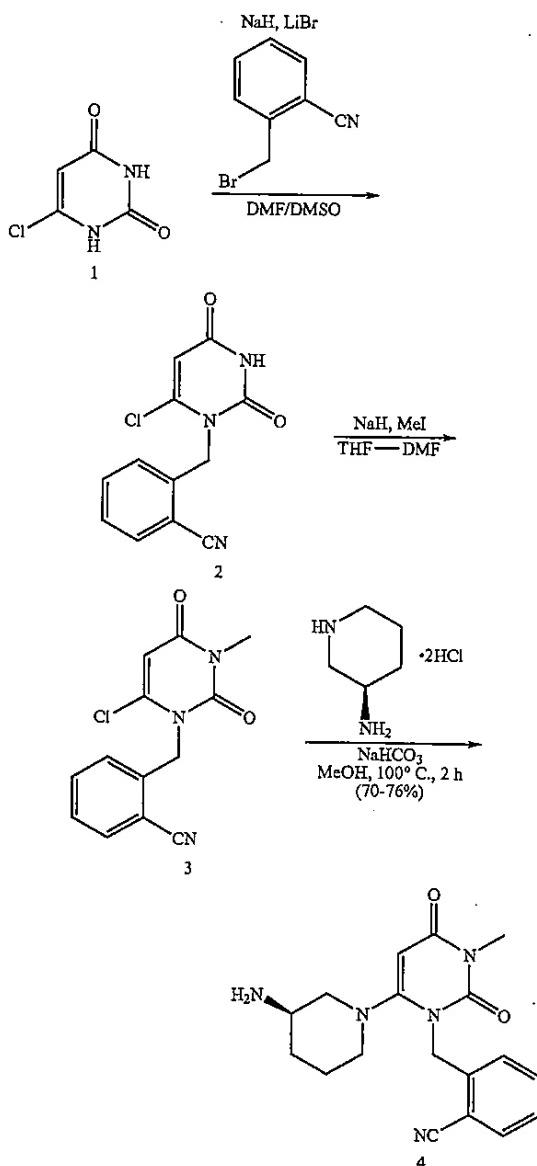
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Descriptions of the syntheses of particular compounds according to the present invention based on the above reaction schemes are set forth herein.

3. Examples of DPP-IV Inhibitors

The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds according to the invention.

Experimental Methods



2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (2). To a solution of 6-chlorouracil (20 g, 122 mmol) in a mixture of DMF-DMSO (6:1, 600 mL) under nitrogen at 0° C., was added sodium hydride (60%, 5.5 g, 137 mmol) in portions. After 0.5 h, lithium bromide (8 g, 96

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mmol) was added into the mixture and stirred for 15 min at 0° C. A solution of α-Bromo-o-tolunitrile (25.1 g, 128 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. It will be understood that alkylation of the amine may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like. The mixture was evaporated and co-evaporated with water in vacuo to remove most of the DMF, and then poured into ice water (1L). The precipitate was collected by filtration. The crude product was suspended in hot AcOEt-CHCl₃ and sonicated for 5 min, allowed to stand at 0° C. for 1 h, and then filtered to give a white solid of the title compound (19 g) in 54% yield. It will also be understood by those skilled in the art that purification may be accomplished using various methods known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography. Non-limiting examples of organic solvents and solvent mixtures may include ethyl acetate, isopropyl acetate, acetone, THF and the like. ¹H-NMR (400 MHz, DMSO): δ 11.82 (s, 1H), 7.87 (d, 1H, J=7.6 Hz), 7.71 (t, 1H, J=7.6 Hz), 7.51 (t, 1H, J=7.6 Hz), 7.37 (d, 1H, J=8 Hz), 6.06 (s, 1H), 5.31 (s, 2H). MS (ES) [m+H] calc'd for C₁₂H₉ClN₃O₂, 262.0; found 262.0.

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (3). To a cold (0° C.) solution of benzylated 6-chlorouracil 2 (10 g, 38 mmol) in DMF-THF (1:1, 300 mL) under nitrogen, was added NaH (60%, 1.6 g, 39.9 mmol) in portions, followed by adding LiBr (2 g). The mixture was stirred at r.t for 20 min. After adding iodomethane (5.4 mL, 76 mmol), the flask was sealed and stirred at this temperature for 10 min, r.t for 2 h, and 35° C. overnight, and then concentrated in vacuo. It will be understood that alkylation of the amine may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like. For example, the alkylation can be performed using methyl iodide and K₂CO₃ in acetone. The reaction may be performed at about 15-45° C., preferably at about 20-43° C., and more preferably at about 35-41° C. until the reaction is complete. The residue was dissolved in CHCl₃ and washed with water and brine, dried (Na₂SO₄), and filtered then concentrated in vacuo. The crude product was crystallized from THF-Hexanes to give 7.6 g (72%) of the title compound 3. It will also be understood by those skilled in the art that the benzonitrile may be purified in a variety of organic solvents or solvent mixtures. For example, the benzonitrile can be purified by adding a mixture of dichloromethane and heptane. Optionally, the benzonitrile may be further purified in an organic solvent or mixture of solvents such as dichloromethane, chloroform, acetonitrile, THF, ethyl acetate, isopropyl acetate and the like. Preferably, the product is purified and washed with ethyl acetate. ¹H NMR (400 MHz, DMSO): δ 7.87 (d, 1H, J=7.6 Hz), 7.70 (t, 1H, J=7.6 Hz), 7.51 (t, 1H, J=7.6 Hz), 7.40 (d, 1H, J=8 Hz), 6.21 (s, 1H), 5.38 (s, 2H), 3.28 (s, 3H). MS (ES) [m+H] calc'd for C₁₃H₁₁ClN₃O₂, 276.1; found 276.1.

2-[6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (4). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (330 mg, 1.08 mmol), (R)-3-amino-piperidine dihydrochloride (246 mg, 1.4 mmol) and sodium

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bicarbonate (500 mg, 5.4 mmol) were stirred with 200 mg activated molecular sieves (4A) in dry MeOH (5 mL) at 100° C. for 2 h. The reaction was filtered through Celite, concentrated in vacuo, and then diluted with CHCl₃, and washed with water. The water phase was extracted with CHCl₃, and the combined organic phases were washed with water, dried (Na₂SO₄), and filtered. TFA (1 mL) was added into the solution which was then concentrated in vacuo. The residue was dissolved in a small amount of MeOH, and Et₂O was added to force precipitation. The mixture was allowed to stand at RT overnight. It will be understood by those skilled in the art that condensation with the amine or amine hydrochloride may be performed in a solvent or mixture of solvents with a base, such as potassium carbonate, sodium bicarbonate and the like, or mixtures thereof. The solvent may comprise both protic and aprotic solvents, or mixtures thereof. For example, the solvent may comprise a mixture of isopropyl alcohol and water. Further, the reaction may be heated to about 30-100° C., preferably about 35-55° C., and more preferably about 45-50° C. until the reaction is complete. Solvents were decanted, and the solid was washed with Et₂O two times to give 270 mg TFA salt of product 4 as off-white powder. It will also be understood that the product may be further purified by washing with an organic solvent or mixture of solvents. Non-limiting examples of solvent or solvent mixtures include isopropyl acetate, ethyl acetate, dichloromethane, heptane, and the like. Further, the product may optionally be purified by column chromatography. The TFA salt of 4 has ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1): δ 7.82 (d, 1H, J=7.6 Hz), 7.65 (t, 1H, J=7.6 Hz), 7.46 (t, 1H, J=7.6 Hz), 7.23 (d, 1H, J=8.0 Hz), 5.42 (s, 1H), 5.50-5.00 (ABq, 2H, J=41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [m+H] calc'd for C₁₈H₂₂N₅O₂, 340.2; found, 340.2.

The benzonitrile product may be isolated as the free base if desired, but preferably, the product may be further converted to a corresponding acid addition salt. For example, the benzoic acid salt was formed by treating the benzonitrile product with benzoic acid to form 2-[6-(3-amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile benzoate (4). Preparation and isolation of the benzoate salt was performed by conventional methods for the formation of acid addition salts.

Following the same procedure described above, HCl addition salt was prepared as follows. A free base form of 4 was isolated after the crude product was washed with water, dried over Na₂SO₄, filtered and concentrated. The free base product was then dissolved in THF. Alternatively, the free base could be dissolved in other solvents, such as dioxane, acetonitrile, ethyl acetate, dichloromethane, etc., or mixtures thereof. The solution was then stirred and 1.2 equivalents of 4M HCl in dioxane was added dropwise. After 10 min stirring, the suspended mixture was allowed to stand at rt for 1 h, and then filtered to give the solid HCl salt form of 4. ¹H-NMR (400 MHz, DMSO-D6): δ 7.82 (d, 1H, J=7.6 Hz), 7.65 (t, 1H, J=7.6 Hz), 7.46 (t, 1H, J=7.6 Hz), 7.23 (d, 1H, J=8.0 Hz), 5.42 (s, 1H), 5.20, 5.08 (ABq, 2H, J=41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H), 2.50 (bs, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [m+H] calc'd for C₁₈H₂₂N₅O₂, 340.2; found, 340.2.

Further, the toluenesulfonate salt was prepared as follows. A 200 μL aliquot of a 0.03M stock solution of free base was dissolved in dichloromethane and concentrated under a slow stream of nitrogen. The resulting free base was dissolved in 150 μL of solvent (e.g., acetic acid, acetone, ethanol, THF or dichloromethane) and the solution shaken for 10 minutes. The shaken solution was then charged with 50 μL of a 0.126M

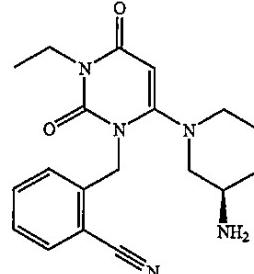
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solution of toluenesulfonic acid (1.05 eq.) in dioxane. The solution was shaken for 3 hours, followed by removal of the solvents under a stream of nitrogen to provide the toluenesulfonate salt.

The toluenesulfonate salt was also prepared by dissolving 2 g of the free base in 10 volumes of acetonitrile and heating the solution to 75° C. for 10 minutes. Then p-toluenesulfonic acid (1.05 equivalents) was added and the solution held at 75° C. for 5 minutes. The temperature was ramped down (at about 25° C./hr) and stirred at room temperature overnight. The product (2.64 g) was dried in a vacuum oven at 50° C. and 698.5 mm Hg with a nitrogen sweep for 18 hours.

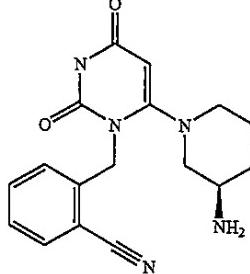
In each of the above steps, the isolation and/or purification steps of the intermediate compounds may be avoided if the intermediates from the reaction mixture are obtained as relatively pure compounds and the by-products or impurities of the reaction mixture do not interfere with the subsequent reaction steps. Where feasible, one or more isolation steps may be eliminated to provide shorter processing times, and the elimination of further processing may also afford higher overall reaction yields.

Compound 5



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2-[6-(3(R)-Amino-piperidin-1-yl)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile TFA salt (5). The title compound, 5, was prepared from sample 2 using the procedures described in the preparation of samples 3 and 4, except that ethyl bromide was used in place of iodomethane. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1): δ 7.66 (d, J=7.8 Hz, 1H), 7.59 (td, J=7.8, 1.4 Hz, 1H), 7.40 (t, J=7.6 Hz, 1H), 7.26 (d, J=7.6 Hz, 1H), 5.41 (s, 1H), 5.13-5.23 (ABq, 2H, J=41.6, 15.2 Hz), 3.91 (q, J=7.1 Hz, 2H), 3.37 (m, 2H), 2.87-2.98 (m, 2H), 2.70 (m, 1H), 2.12 (m, 1H), 1.88 (m, 1H), 1.67 (m, 2H), 1.15 (t, J=6.9 Hz, 3H). MS (ES) [m+H] calc'd for C₁₉H₂₄N₅O₂, 354.2; found, 354.2.

Compound 6

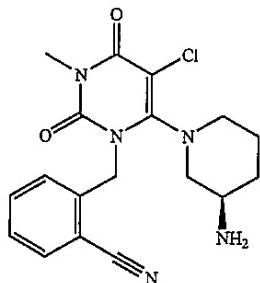


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2-[6-(3(R)-Amino-piperidin-1-yl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (6). The title compound 6 was prepared from compound 2 by the procedure

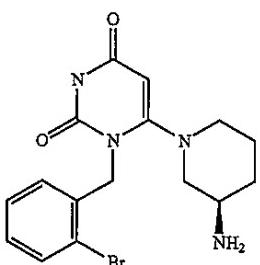
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used in preparation of compound 4. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1): δ 7.65 (d, J=7.5 Hz, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.39 (t, J=7.5 Hz, 1H), 7.27 (d, J=7.8 Hz, 1H), 5.32 (s, 1H), 5.13-5.13 (ABq, 2H, J=30.0, 15.0 Hz), 3.39 (m, 2H), 2.95 (m, 2H), 2.69 (m, 1H), 2.12 (m, 1H), 1.85 (m, 1H), 1.64 (m, 2H). MS (ES) [m+H] calc'd for C₁₇H₂₀N₅O₂, 326.2; found, 326.2.



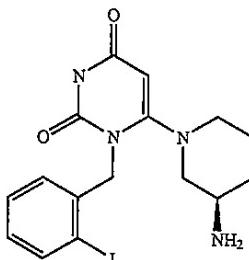
2-[6-(3(R)-Amino-piperidin-1-yl)-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (7). Compound 4 (40 mg, 0.1 mmol) in CHCl₃ (2 mL) was treated with SOCl₂ (200 μL) at 100° C. for 30 min, concentrated, and then purified by LC-MS to give the title compound 7. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1): δ 7.73 (d, J=7.6 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.14 (d, J=8.1 Hz, 1H), 5.32-5.42 (m, 2H), 3.43 (s, 3H), 3.33-3.40 (m, 2H), 3.17 (m, 2H), 2.87 (s, 1H), 2.08 (m, 1H), 1.70 (m, 1H), 1.32-1.43 (m, 2H). MS (ES) [m+H] calc'd for C₁₈H₂₁ClN₅O₂, 374.1; found, 374.1.



6-[3-(R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione (8). The title compound was prepared in two steps. The first step was accomplished using the procedure for the preparation of compound 2, except that 2-bromobenzylbromide was used in the place of α-Bromo-o-tolunitrile. The crude product was then converted to the title compound by the method used in the preparation of compound 4. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1): δ 7.52 (d, J=8.1 Hz, 1H), 7.24 (t, J=7.8 Hz, 1H), 7.10 (t, J=7.8 Hz, 1H), 6.89 (d, J=7.579 Hz, 1H), 5.27 (s, 1H), 4.92-5.04 (ABq, J=34.1, 15.0 Hz, 2H), 3.27 (bd, J=10.4 Hz, 1H), 3.09-3.18 (m, 1H), 2.89 (m, 1H), 2.70 (t, J=10.9 Hz, 1H), 2.48 (t, J=12.0 Hz, 1H), 2.03 (m, 1H), 1.60-1.71 (m, 1H), 1.42-1.53 (m, 2H). MS (ES) [m+H] calc'd for C₁₆H₂₀BrN₄O₂, 379.1; found, 379.1.

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Compound 9



Compound 7

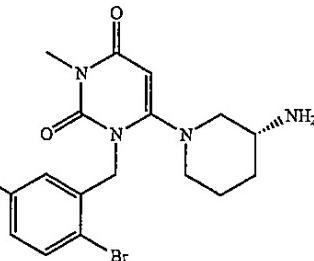
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6-[3-(R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione (9). The title compound was prepared by the procedure described in the preparation of compound 8, except that 2-iodobenzyl chloride was used as the benzylating reagent. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1): δ 7.76 (d, J=7.6 Hz, 1H), 7.21 (t, J=7.3 Hz, 1H), 6.89 (t, J=7.2 Hz, 1H), 6.79 (d, J=7.3 Hz, 1H), 5.26 (s, 1H), 4.79-4.92 (ABq, J=34.1, 6.70 Hz, 2H), 3.27 (m, 1H), 3.13 (s, 1H), 2.85 (d, J=11.6 Hz, 1H), 2.70 (m, 1H), 2.41 (m, 1H), 2.02 (m, 1H), 1.60 (m, 1H), 1.45 (m, 2H). MS (ES) [m+H] calc'd for C₁₆H₂₀IN₄O₂, 427.1; found, 427.1.

Compound 10



Compound 8

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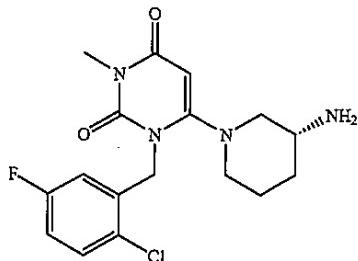
6-[3-(R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluorobenzyl)-1H-pyrimidine-2,4-dione (10). To a solution of 6-chlorouracil (220 mg, 1.5 mmol) in a mixture of dry DMF-DMSO (6:1, 5 mL) under nitrogen at 0° C., was added sodium hydride (60%, 61 mg, 1.8 mmol) in portions. After 0.5 h, lithium bromide (83 mg, 1 mmol) was added and the mixture was stirred for 15 min at 0° C. A solution of 2-bromo-5-fluorobenzyl bromide (497 mg, 1.8 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. The mixture was evaporated and co-evaporated with water in vacuo to remove most of the DMF, and then poured into ice-water. The precipitate was collected by filtration, and then suspended in cold MeOH and filtered. The solution was concentrated to give the crude monobenzylated product.

The crude product was treated with NaH and MeI using the procedure described in the preparation of compound 3, followed by the procedure used in the preparation of compound 4 to give the title compound. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ 7.46 (dd, J=8.7, 5.2 Hz, 1H), 6.82 (td, J=8.3, 2.9 Hz, 1H), 6.59 (dd, J=9.1, 3.0 Hz, 1H), 5.28 (s, 1H), 4.99-5.06 (ABq, J=41.7, 16.7 Hz, 2H), 3.28 (m, 1H), 3.23 (s, 3H), 3.13-3.21 (m, 1H), 2.86 (bd, J=12.6 Hz, 1H), 2.71 (t,

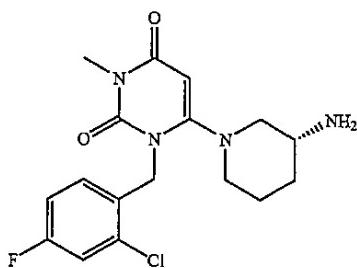
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$J=10.5$ Hz, 1H), 2.47 (t, $J=11.0$ Hz, 1H), 2.00-2.08 (m, 1H), 1.65-1.74 (m, 1H), 1.42-1.53 (m, 2H). MS (ES) [m+H] calc'd for $C_{17}H_{21}BrFN_4O_2$, 411.1; found, 411.1.



6-[3-(R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluorobenzyl)-3-methyl-1H-pyrimidine-2,4-dione (11). The title compound was prepared from compound 1 using the same procedures as the preparation of compound 10, except that 2-chloro-5-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1): δ 7.34-7.40 (dd, $J=8.5$, 5.1 Hz, 1H), 6.97 (td, $J=8.3$, 2.9 Hz, 1H), 6.72 (dd, $J=9.0$, 2.9 Hz, 1H), 5.41 (s, 1H), 5.11-5.19 (ABq, $J=41.7$, 16.7 Hz, 2H), 3.37 (s, 1H), 3.32 (s, 3H), 3.23-3.30 (m, 1H), 2.96 (d, $J=12.1$ Hz, 1H), 2.81 (t, $J=10.2$ Hz, 1H), 2.59 (t, $J=11.1$ Hz, 1H), 2.13 (d, $J=10.4$ Hz, 1H), 1.76-1.86 (m, 1H), 1.52-1.63 (m, 2H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found, 367.1.

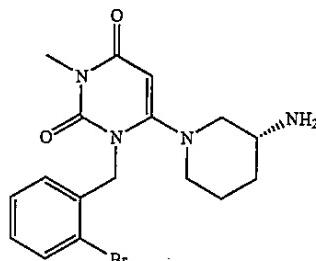


6-[3-(R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluorobenzyl)-3-methyl-1H-pyrimidine-2,4-dione (12). The title compound was prepared from compound 1 using the same procedures as described the preparation of compound 10, except that 2-chloro-4-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1) δ 7.15 (dd, $J=8.211$, 2.400 Hz, 1H), 6.95-7.06 (m, 2H), 5.40 (s, 1H), 5.09-5.18 (ABq, $J=37.7$, 15.9 Hz, 2H), 3.33-3.39 (m, 1H), 3.30 (s, 3H), 3.23-3.29 (m, 1 H), 2.98 (bd, $J=12.9$ Hz, 1H), 2.79 (t, $J=10.4$ Hz, 1H), 2.55-2.66 (t, $J=11.2$ Hz, 1H), 2.13 (m, 1H), 1.78-1.88 (m, 1H), 1.55-1.65 (m, 2H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found 367.1.

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Compound 11

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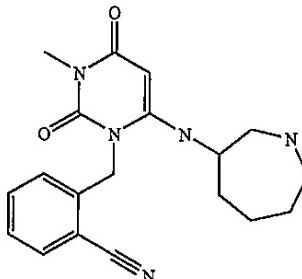
Compound 13



15 6-[3-(R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (13). The title compound was prepared from compound 1 used the procedures described in the synthesis of compound 10, except that 2-bromo benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1): δ 7.45 (d, $J=7.8$ Hz, 1H), 7.16 (t, $J=7.5$ Hz, 1H), 7.03 (t, $J=7.2$ Hz, 1H), 6.80 (d, $J=7.3$ Hz, 1H), 5.28 (s, 1H), 4.93-5.05 (ABq, 2H, $J=36.4$, 16.4 Hz), 3.22 (m, 1H), 3.19 (m, 3H), 3.09 (m, 1H), 2.84 (d, $J=12.6$ Hz, 1H), 2.63 (t, $J=10.5$ Hz, 1H), 2.42 (t, $J=10.9$ Hz, 1H), 1.97 (d, $J=11.1$ Hz, 1H), 1.58-1.69 (m, 1H), 1.38-1.48 (m, 2H). MS (ES) [m+H] calc'd for $C_{17}H_{22}BrN_4O_2$, 393.1; found, 393.1.

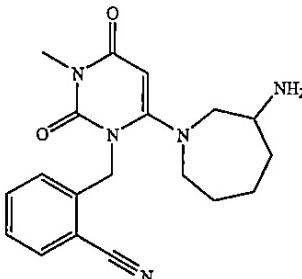
30 Compound 12

Compound 14



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Compound 15



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2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14) and 2-{6-[3-(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (15). Title compounds 14 and 15 were prepared from compound 3 (70 mg, 0.27 mmol) and azepan-3-ylamine (70 mg, 0.61 mg) using the procedure for the preparation of compound 4. Both compounds were purified by LC-MS.

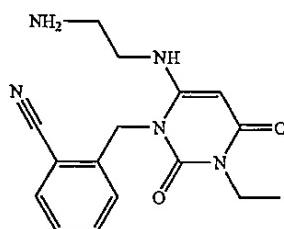
14: 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1) δ 7.77 (d, $J=7.8$ Hz, 1H), 7.66 (t, $J=7.6$ Hz, 1H), 7.47 (t, $J=8.0$ Hz, 1H), 7.36 (d, $J=8.1$ Hz, 1H), 5.54 (s, 1H), 5.49 (s, 1H), 5.27-5.36 (ABq, $J=26.0$, 16.4 Hz, 2H), 3.50 (m, 2H), 3.37 (s, 2H), 3.26

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(s, 3H), 3.12 (m, 1H), 3.04 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.60-1.71 (m, 3H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

15: 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1) δ 7.77 (d, J=8.1 Hz, 1H), 7.63 (t, J=7.6 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.19 (d, J=7.6 Hz, 1H), 5.48 (s, 1H), 5.44-5.52 (ABq, J=61.9, 18.4 Hz, 2H), 3.80 (s, 1H), 3.58-3.50 (m, 1H), 3.39-3.39 (m, 1H), 3.26 (s, 3H), 3.13 (m, 1H), 2.89 (t, J=12.4 Hz, 1H), 2.04 (m, 1H), 1.93 (m, 1H), 1.86 (m, 2H), 1.59-1.70 (m, 2H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.



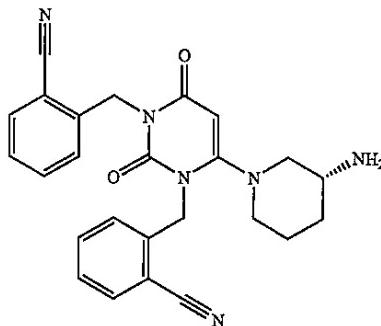
Compound 16

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Compound 18



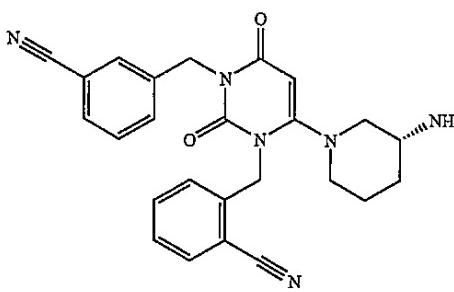
2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (16). Compound 2 (150 mg, 0.57 mmol) in THF-DMSO (6:1, 4 mL) was treated with 60% NaH (26 mg, 0.65 mmol), followed by adding ethyl bromide (300 μ L). In a sealed tube, ~20% crude product in dry MeOH (3 mL) was treated $NaHCO_3$ and ethane-1,2-diamine (200 μ L) at 120° C. for 2 h, and purified by LC-MS to give the title compound 16. 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1) δ 7.70 (d, J=7.8 Hz, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.40 (t, J=7.4 Hz, 1H), 7.12 (d, J=8.1 Hz, 1H), 5.37 (s, 2H), 3.95 (q, J=6.8 Hz, 2H), 3.45 (t, J=5.9 Hz, 2H), 3.11 (t, J=6.1 Hz, 2H), 1.19 (t, J=6.8 Hz, 3H). MS (ES) [m+H] calc'd for $C_{16}H_{20}N_5O_2$, 314.2; found 314.2.

25 2-[6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (18). Title compound 18 was prepared by the methods used in the preparation of compound 17, except that α -bromo-o-tolunitrile was used in the place of m-cyano-benzyl bromide. 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1) δ 7.64 (d, J=6.8 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.55 (t, J=7.8 Hz, 2H), 7.44 (t, J=7.6 Hz, 1H), 7.38 (t, J=7.5 Hz, 1H), 7.31 (t, J=7.6 Hz, 1H), 7.27 (d, J=7.8 Hz, 1H), 7.12 (d, J=7.8 Hz, 1H), 5.45 (s, 1H), 5.15-5.32 (m, 4H), 3.36-3.47 (m, 2H), 2.98 (m, 2H), 2.10 (m, 1H), 1.91 (m, 1H), 1.68 (m, 2H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 17

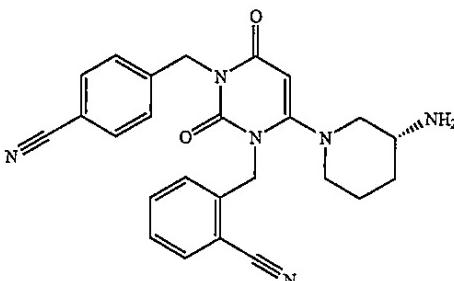
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Compound 19



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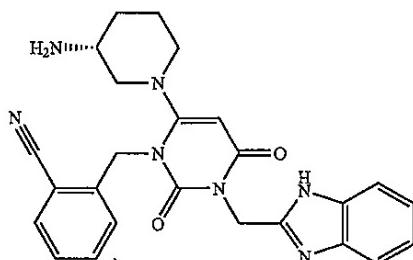


2-[6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (17). Compound 2 (65 mg, 0.25 mmol) in DME-DMF (2:1, 2.5 mL) was treated with 60% NaH (15 mg, 0.38 mmol) at 0° C. for 20 min, and then LiBr (25 mg) was added. 10 min later, m-cyano-benzyl bromide (55 mg, 0.28 mg) was added, and the mixture was stirred at RT for 5 h, and concentrated. The crude residue was dissolved in MeOH (3 mL). (R)-3-Amino-piperidine dihydrochloride (52 mg, 0.3 mmol) and sodium bicarbonate (100 mg) were added. The mixture was heated in a sealed tube at 120° C. for 2 h, and then filtered and concentrated. LC-MS purification gave the title compound 17 in 84% yield. 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1) δ 7.67 (d, J=7.8 Hz, 1H), 7.52-7.62 (m, 4H), 7.35-7.46 (m, 2H),

55 2-[6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (19). Title compound 19 was prepared by the methods used in the preparation of compound 17, except that p-cyano-benzyl bromide was used in the place of m-cyano-benzyl bromide. 1H -NMR (400 MHz, $CDCl_3$ - CD_3OD 10:1) δ 7.70 (d, J=7.8 Hz, 1H), 7.56-7.63 (m, 3H), 7.46 (m, 3H), 7.29 (d, J=7.8 Hz, 1H), 5.47 (s, 1H), 5.16-5.36 (ABq, J=51.1, 14.7 Hz, 2H), 5.11 (s, 2H), 3.36-3.47 (m, 2H), 2.90-3.07 (m, 2H), 2.79 (s, 1 H), 2.15 (s, 1H), 1.95 (s, 1H), 1.73 (s, 2H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

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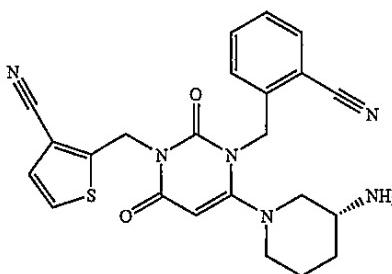
Compound 20

2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (20). Title compound 20 was prepared by the methods used in the preparation of compound 17, except that 2-chloromethyl benzimidazole was used in the place of m-cyano-benzyl bromide. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ 7.67 (d, J=3.0 Hz, 1H), 7.65-7.56 (m, 2H), 7.47 (d, J=3.3 Hz, 2H), 7.46 (d, J=3.3 Hz, 1H), 7.37-7.40 (m, 2H), 5.52 (s, 3H), 5.23 (s, 2H), 3.51 (d, J=9.6 Hz, 1H), 3.36 (m, 1H), 2.87-2.92 (m, 2H), 2.64-2.72 (m, 1H), 2.09 (m, 1H), 1.76 (m, 1H), 1.52-1.64 (m, 2H). MS (ES) [m+H] calc'd for C₂₅H₂₆N₇O₂, 456.2; found 456.2.

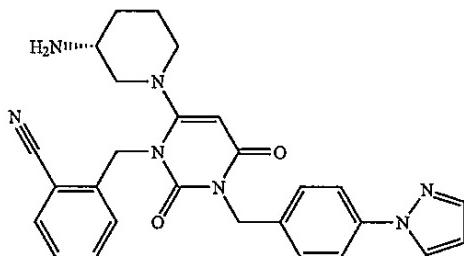
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zonitrile (22). Title compound 22 was prepared by the methods used in the preparation of compound 17, except that 1-(3-bromomethyl-phenyl)-1H-pyrrole was used in the place of m-cyano-benzyl bromide. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ 7.59 (d, J=7.3 Hz, 1H), 7.48 (t, J=7.7 Hz, 1H), 7.24-7.36 (m, 4H), 7.21 (t, J=7.6 Hz, 2H), 7.02 (t, J=2.1 Hz, 2H), 6.32 (t, J=2.0 Hz, 2H), 5.42 (s, 1H), 5.11-5.20 (ABq, J=44.7, 15.9 Hz, 2H), 5.06 (s, 2H), 3.36 (m, 2H), 2.98 (m, 1H), 2.89 (m, 1H), 2.70 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.73-1.58 (m, 2H). MS (ES) [m+H] calc'd for C₂₈H₂₉N₆O₂, 481.2; found 481.2.

Compound 23

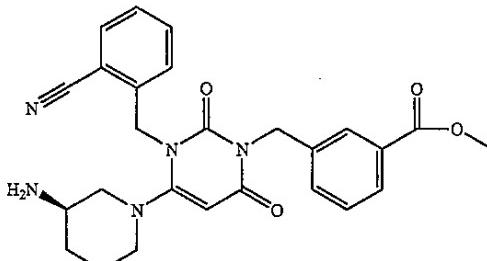


Compound 21

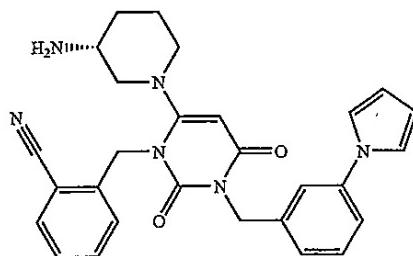


2-[6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (21). Title compound 21 was prepared by the methods used in the preparation of compound 17, except that 1-(4-bromomethyl-phenyl)-1H-pyrazole was used in the place of m-cyano-benzyl bromide. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ 7.90 (d, J=2.5 Hz, 1H), 7.71 (d, J=1.8 Hz, 1H), 7.65 (d, J=7.6 Hz, 1H), 7.51-7.58 (m, 3H), 7.43-7.37 (m, 3H), 7.22 (d, J=7.8 Hz, 1H), 6.47 (t, J=2.1 Hz, 1H), 5.43 (s, 1H), 5.14-5.30 (ABq, J=41.2, 16.4 Hz, 2H), 5.05 (s, 2H), 3.32-3.40 (m, 2H), 2.96 (m, 1H), 2.89 (m, 1H), 2.70 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.66 (s, 2H). MS (ES) [m+H] calc'd for C₂₇H₂₈N₇O₂, 482.2; found 482.2.

Compound 24



Compound 22



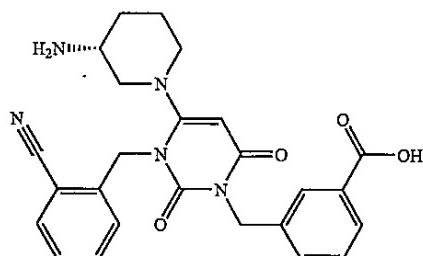
2-[6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-ben-

zonitrile (22). Title compound 22 was prepared by the methods used in the preparation of compound 17, except that 3-bromomethyl-benzoic acid methyl ester was used in the place of m-cyano-benzyl bromide. ¹H-NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ 7.99 (s, 1H), 7.91 (d, J=7.8 Hz, 1H), 7.65 (d, J=7.6 Hz, 1H), 7.56 (d, J=7.9 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.34 (t, J=7.6 Hz, 1H), 7.23 (d, J=8.1 Hz, 1H), 5.44 (s, 1H), 5.12-5.31 (ABq, J=43.7, 15.9 Hz, 2H), 5.08 (s, 2H), 3.90 (s, 3H), 3.31-3.39 (m, 2H), 2.98 (d, J=11.9 Hz, 1H), 2.87 (m, 1H), 2.71 (m, 1H), 2.11 (m, 1H),

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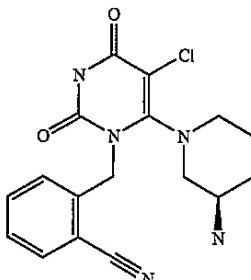
1.89 (m, 1 H), 1.73-1.59 (m, 2H). MS (ES) [m+H] calc'd for $C_{26}H_{28}N_5O_4$, 474.2; found 474.2.



Compound 25

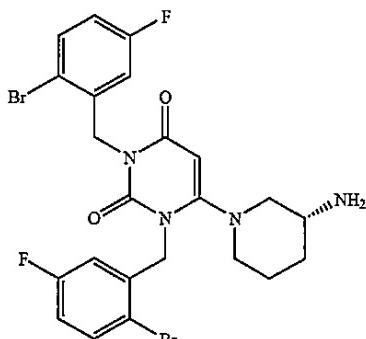
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Compound 27



2-[{3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (27). Compound 4 (100 mg) in THF (2 mL) was treated with 4M HCl in dioxane (1 mL) at rt for 1 h, concentrated, and then purified by LC-MS to give the title compound. 1H -NMR (400 MHz, DMSO-D₆): δ ppm 12.0 (s, 1H), 7.88 (d, J =7.6 Hz, 1H), 7.68 (t, J =7.7 Hz, 1H), 7.49 (t, J =7.7 Hz, 1H), 7.36 (d, J =7.8 Hz, 1H), 5.09-5.21 (m, 2H), 3.17 (m, 2H), 2.96 (t, J =11.1 Hz, 1H), 2.86 (d, J =10.6 Hz, 1H), 2.65 (m, 1H), 1.90 (d, J =11.6 Hz, 1H), 1.57 (d, J =13.1 Hz, 1H), 1.19-1.31 (m, 1H), 1.03-1.15 (m, 1H). MS (ES) [m+H] calc'd for $C_{17}H_{19}ClN_5O_2$, 360.1; found, 360.1.

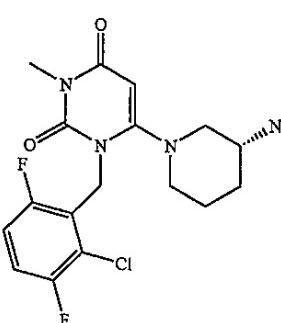
3-[4-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-benzoic acid (25). A crude mixture of compound 24 (~50 mg) was treated with LiOH in THF-water (10:1) to give the title compound 25. 1H -NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ 7.90 (s, 1H), 7.86 (d, J =7.6 Hz, 1H), 7.60 (d, J =7.6 Hz, 1H), 7.50 (t, J =8.2 Hz, 1H), 7.45 (d, J =7.3 Hz, 1H), 7.26-7.36 (m, 2H), 7.17 (d, J =8.1 Hz, 1H), 5.39 (s, 1H), 5.10-5.25 (ABq, J =36.9, 15.5 Hz, 2H), 5.03 (s, 2H), 3.31 (m, 2H), 2.95 (m, 1H), 2.81 (m, 1H), 2.64 (m, 1H), 2.07 (m, 1H), 1.82 (m, 1H), 1.51-1.68 (m, 2H). MS (ES) [m+H] calc'd for $C_{25}H_{26}N_5O_4$, 460.2; found 460.2.



Compound 26

6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-di-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (28). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2,5-di-chlorobenzyl bromide was used in the place of 2-bromo-5-fluorobenzyl bromide. 1H -NMR (400 MHz, CDCl₃-CD₃OD 10:1): δ ppm 7.50 (d, J =8.6 Hz, 1H), 7.39 (dd, J =8.3, 2.526 Hz, 1H), 7.22 (d, J =2.5 Hz, 1H), 5.41 (s, 1H), 5.01-4.93 (ABq, J =41.9, 16.2 Hz, 2H), 3.25 (m, 2H), 3.10 (s, 3H), 2.85 (m, 1H), 2.76 (m, 1 H), 2.67 (m, 1H), 1.91 (m, 1H), 1.75 (m, 1H), 1.45 (m, 2H). MS (ES) [m+H] calc'd for $C_{17}H_{21}Cl_2N_4O_2$, 383.1; found 383.1.

6-[3 (R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione (26). The title compound was prepared from 1 by di-benzylation, using the procedure for the preparation of 2, except that 2-bromo-5-fluorobenzyl bromide was used in the place of α -bromo- ω -tolunitrile, followed by treatment with 3-(R)-amino-piperidine under the conditions described in the preparation of compound 4. 1H -NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ 7.42 (dd, J =8.6, 5.3 Hz, 2H), 7.11-7.08 (dd, J =9.1, 2.2 Hz, 1H), 7.06 (dd, J =9.3, 2.8 Hz, 1H), 6.78-6.84 (m, 2H), 5.71 (s, 1H), 5.29 (s, 4H), 4.22 (d, J =11.1 Hz, 1H), 3.82 (d, J =13.4 Hz, 1H), 3.07-3.24 (m, 3H), 2.06 (m, 1H), 1.75-1.83 (m, 1H), 1.63-1.72 (m, 1H), 1.50-1.59 (m, 1H). MS (ES) [m+H] calc'd for $C_{23}H_{23}Br_2F_2N_3O_2$, 583.01; found 583.01.



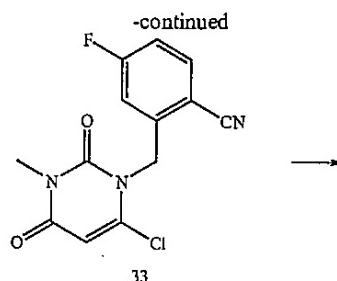
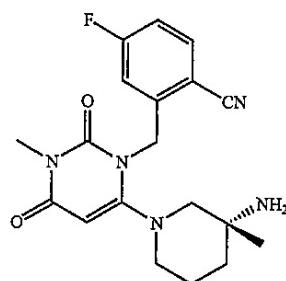
Compound 29

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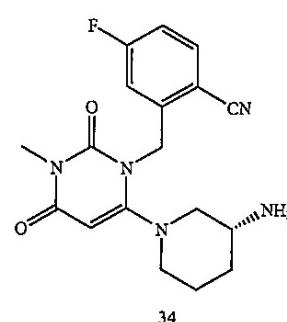
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6-[3-(R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-difluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (29). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2-chloro-3,6-di-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ¹H NMR (400 MHz, CDCl₃-CD₃OD 10:1) δ ppm 6.98-7.06 (m, 2H), 6.90 (m, 2H), 5.31 (s, 1H), 5.01-5.20 (ABq, J=24.2, 14.4 Hz, 2H), 3.28-3.37 (m, 2H), 3.13 (s, 3H), 3.01-2.94 (m, 1H), 2.6-2.9 (m, 2H), 2.10 (m, 1H), 1.92 (m, 2H), 1.73 (s, 1H), 1.6-1.75 (m, 2H). MS (ES) [m+H] calc'd for C₁₇H₂₀ClF₂N₄O₂, 385.1; found 385.1.

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Compound 30

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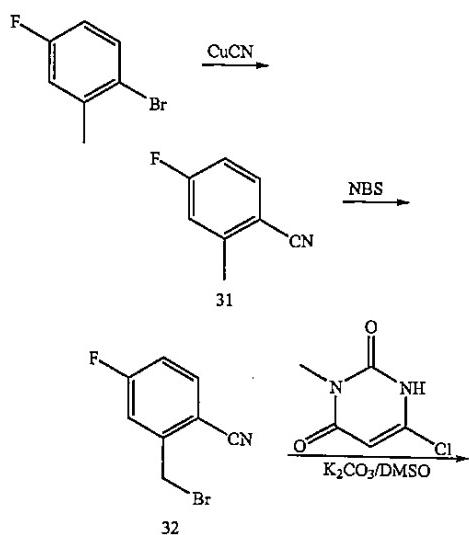
(R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile (30). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (R)-3-amino-3-methyl-piperidine dihydrochloride (266 mg, 1.4 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100° C. for 2 hrs. The final compound was obtained as TFA salt after HPLC purification. ¹H-NMR (400 MHz, CD₃OD): δ 7.78-7.83 (m, 1H), 7.14-7.26 (m, 2H), 5.47 (s, 1H), 5.12-5.36 (ABq, 2H, J=105.2, 15.6 Hz), 3.21 (s, 1H), 2.72-3.15 (m, 4H), 1.75-1.95 (m, 4H), 1.39 (s, 3H). MS (ES) [m+H] calc'd for C₁₉H₂₂FN₅O₂, 372.41; found, 372.41.

30 4-Fluoro-2-methylbenzonitrile (31). A mixture of 2-bromo-5-fluorotoluene (3.5 g, 18.5 mmol) and CuCN (2 g, 22 mmol) in DMF (100 mL) was refluxed for 24 hours. The reaction was diluted with water and extracted with hexane. The organics were dried over MgSO₄ and the solvent removed to give product 31 (yield 60%). ¹H-NMR (400 MHz, CDCl₃): δ 7.60 (dd, J=5.6, 8.8 Hz, 1H), 6.93-7.06 (m, 2H), 2.55 (s, 3H).

2-Bromomethyl-4-fluorobenzonitrile (32). A mixture of 4-fluoro-2-methylbenzonitrile (2 g, 14.8 mmol), NBS (2.64 g, 15 mmol) and AIBN (100 mg) in CCl₄ was refluxed under nitrogen for 2 hours. The reaction was cooled to room temperature. The solid was removed by filtration. The organic solution was concentrated to give crude product as an oil, which was used in the next step without further purification. ¹H-NMR (400 MHz, CDCl₃): δ 7.68 (dd, J=5.2, 8.4 Hz, 1H), 7.28 (dd, J=2.4, 8.8 Hz, 1H), 7.12 (m, 1H), 4.6 (s, 2H).

45 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (33). A mixture of 50 crude 3-methyl-6-chlorouracil (0.6 g, 3.8 mmol), 2-bromomethyl-4-fluorobenzonitrile (0.86 g, 4 mmol) and K₂CO₃ (0.5 g, 4 mmol) in DMSO (10 mL) was stirred at 60° C. for 2 hours. The reaction was diluted with water and extracted with EtOAc. The organics were dried over MgSO₄ and the solvent removed. The residue was purified by column chromatography. 0.66 g of the product was obtained (yield: 60%). ¹H-NMR (400 MHz, CDCl₃): δ 7.73 (dd, J=7.2, 8.4 Hz, 1H), 7.26 (d, J=4.0 Hz, 1H), 7.11-7.17 (m, 1H), 6.94 (dd, J=2.0, 9.0 Hz, 1H), 6.034 (s, 2H), 3.39 (s, 3H). MS (ES) [m+H] calc'd for C₁₃H₉ClFN₃O₂, 293.68; found 293.68.

55 2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile (34). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (R)-3-amino-piperidine dihydrochloride (266 mg, 1.5 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100° C. for 2 hrs.



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The final compound was obtained as TFA salt after HPLC purification. ¹H-NMR (400 MHz, CD₃OD): δ 7.77-7.84 (m, 1H), 7.16-7.27 (m, 2H), 5.46 (s, 1H), 5.17-5.34 (ABq, 2H, J=35.2, 15.6 Hz), 3.33-3.47 (m, 2H), 3.22 (s, 3H), 2.98-3.08 (m, 1H), 2.67-2.92 (m, 2H), 2.07-2.17 (m, 1H), 1.82-1.92 (m, 1H), 1.51-1.79 (m, 2H). MS (ES) [m+H] calc'd for C₁₈H₂₀FN₅O₂, 357.38; found, 357.38.

The TFA salt (34) was suspended in DCM, and then washed with saturated Na₂CO₃. The organic layer was dried and removed in vacuo. The residue was dissolved in acetonitrile and HCl in dioxane (1.5 eq.) was added at 0° C. The HCl salt was obtained after removing the solvent. ¹H-NMR (400 MHz, CD₃OD): δ 7.77-7.84 (m, 1H), 7.12-7.26 (m, 2H), 5.47 (s, 1H), 5.21-5.32 (ABq, 2H, J=32.0, 16.0 Hz), 3.35-3.5 (m, 2H), 3.22 (s, 3H), 3.01-3.1 (m, 1H), 2.69-2.93 (m, 2H), 2.07-2.17 (m, 1H), 1.83-1.93 (m, 1H), 1.55-1.80 (m, 2H). MS (ES) [m+H] calc'd for C₁₈H₂₀FN₅O₂, 357.38; found, 357.38.

The product was also converted to a variety of corresponding acid addition salts. Specifically, the benzonitrile product (approximately 10 mg) in a solution of MeOH (1 mL) was treated with various acids (1.05 equivalents). The solutions were allowed to stand for three days open to the air. If a precipitate formed, the mixture was filtered and the salt dried. If no solid formed, the mixture was concentrated in vacuo and the residue isolated. In this way, salts of 34 were prepared from the following acids: benzoic, p-toluenesulfonic, succinic, R-(--)-Mandelic and benzenesulfonic. The succinate was found to be crystalline as determined by x-ray powder diffraction analysis.

In addition, the methanesulfonate salt was prepared as follows. A 10.5 g aliquot of the benzonitrile product was mixed with 400 mL of isopropylacetate. The slurry was heated to 75° C. and filtered through #3 Whatman filter paper. The solution was heated back to 75° C. and a 1M solution of methanesulfonic acid (30.84 mL) was added slowly over 10 minutes while stirring. The suspension was cooled to room temperature at a rate of about 20° C./hr. After 1 hr at room temperature, the solid was filtered and dried in an oven overnight to obtain the methanesulfonate salt.

Examples of In Vitro Assays

The protease inhibitory activities of DPP-IV inhibitors can be readily determined by methods known to those of ordinary skill in the art since suitable in vitro assays for measuring protease activity and the inhibition thereof by test compounds are known. Examples of assays that may be used for measuring protease inhibitory activity and selectivity are set forth below.

DPP-IV Assay

Solutions of test compounds in varying concentrations (≤ 10 mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20 mM Tris, pH 7.4; 20 mM KCl; and 0.1 mg/mL BSA. Human DPP-IV (0.1 nM final concentration) was added to the dilutions and pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with A-P-7-amido-4-trifluoromethylcoumarin (AP-AFC; 10 μ M final concentration). The total volume of the reaction mixture was 10-100 μ L depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation $\lambda=400$ nm; emission $\lambda=505$ nm) for 5-10 minutes or an endpoint was measured after 10 minutes. Inhibition constants (IC₅₀) were calculated from the enzyme progress curves using standard mathematical models.

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FAP α Assay

Solutions of test compounds in varying concentrations (≤ 10 mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20 mM Tris, pH 7.4; 20 mM KCl; and 0.1 mg/mL BSA. Human FAP α (2 nM final concentration) was added to the dilutions and pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with A-P-7-amido-4-trifluoromethylcoumarin (AP-AFC; 40 μ M final concentration). The total volume of the reaction mixture was 10-100 μ L depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation $\lambda=400$ nm; emission $\lambda=505$ nm) for 5-10 minutes or an endpoint was measured after 10 minutes. Inhibition constants (IC₅₀) were calculated from the enzyme progress curves using standard mathematical models.

PREP Assay

Solutions of test compounds in varying concentrations (≤ 10 mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 20 mM Sodium Phosphate, pH 7.4; 0.5 mM EDTA; 0.5 mM DTT; and 0.1 mg/mL BSA. PREP (EC3.4.21.26 from Flavobacterium meningosepticum; 0.2 nM final concentration) was added to the dilutions. The PREP and compound were pre-incubated for 10 minutes at ambient temperature before the reaction was initiated with Z-G-P-AMC (10 μ M final concentration). The total volume of the reaction mixture was 10-100 μ L depending on assay formats used (384 or 96 well plates). The reaction was followed kinetically (excitation $\lambda=375$ nm; emission $\lambda=460$ nm) for 10 minutes or an endpoint was measured after 10 minutes. Inhibition constants (IC₅₀) were calculated from the enzyme progress curves using standard mathematical models.

Tryptase Assay

Solutions of test compounds in varying concentrations (≤ 10 mM final concentration) were prepared in Dimethyl Sulfoxide (DMSO) and then diluted into assay buffer comprising: 100 mM Hepes, pH 7.4; 0.01% Brij35; and 10% glycerol. Tryptase (rhLung beta; 0.1 nM final concentration) was added to the dilutions and pre-incubated with compound for 10 minutes at ambient temperature. The enzymatic reaction was initiated with 25 μ M Z-lys-SBzl and 400 μ M DTNB. The total volume of the reaction mixture was 100 μ L in Costar A/2 96 well plates. The reaction was followed calorimetrically ($\lambda=405$ nm) for 10 minutes. Inhibition constants (IC₅₀) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective DPP-IV inhibitory activity. For example, compounds of the invention were found to inhibit DPP-IV activity at concentrations that are at least 50 fold less than those concentrations required to produce an equiactive inhibition of protease activity for FAP α . The apparent inhibition constants (K_i) for compounds of the invention, against DPP-IV, were in the range from about 10⁻⁹M to about 10⁻⁵M.

It will be apparent that various modifications and variations can be made to the compounds, compositions, kits, and methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

US 7,807,689 B2

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binder, adjuvants, carriers, wetting agents, emulsifying agents, solubilizing agents and pH buffering agents.

14. The pharmaceutical composition according to claim 13, wherein the composition is a solid formulation adapted for oral administration.

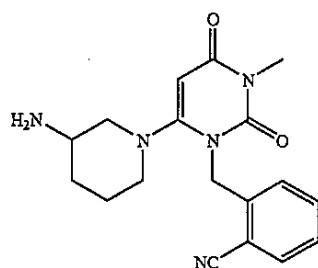
15. The pharmaceutical composition according to claim 13, wherein the composition is a tablet.

16. The pharmaceutical composition according to claim 13, wherein the composition is a liquid formulation adapted for oral administration.

17. The pharmaceutical composition according to claim 13, wherein the composition is a liquid formulation adapted for parenteral administration.

18. The pharmaceutical composition according to claim 13, wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery, subcutaneously, intraadiposally, intraarticularly, and intrathecally.

19. A pharmaceutical composition comprising, as an active ingredient, a compound of the formula



wherein the compound is present in a free base form, and one or more compounds selected from the group consisting of excipients, diluents, lubricants, binders, adjuvants, carriers, wetting agents, emulsifying agents, solubilizing agents and pH buffering agents.

20. The pharmaceutical composition according to claim 19, wherein the composition is a solid formulation adapted for oral administration.

21. The pharmaceutical composition according to claim 19, wherein the composition is a tablet.

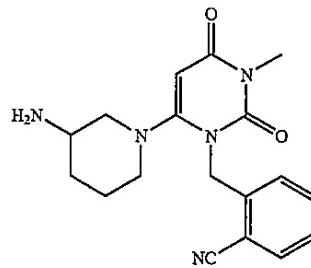
22. The pharmaceutical composition according to claim 19, wherein the composition is a liquid formulation adapted for oral administration.

23. The pharmaceutical composition according to claim 19, wherein the composition is a liquid formulation adapted for parenteral administration.

24. The pharmaceutical composition according to claim 19, wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery, subcutaneously, intraadiposally, intraarticularly, and intrathecally.

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25. A pharmaceutical composition comprising, as an active ingredient, a compound of the formula



wherein the compound is present as a benzoate salt, and one or more compounds selected from the group consisting of excipients, diluents, lubricants, binders, adjuvants, carriers, wetting agents, emulsifying agents, solubilizing agents and pH buffering agents.

26. The pharmaceutical composition according to claim 25, wherein the composition is a solid formulation adapted for oral administration.

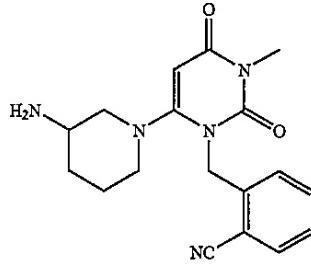
27. The pharmaceutical composition according to claim 25, wherein the composition is a tablet.

28. The pharmaceutical composition according to claim 25, wherein the composition is a liquid formulation adapted for oral administration.

29. The pharmaceutical composition according to claim 25, wherein the composition is a liquid formulation adapted for parenteral administration.

30. The pharmaceutical composition according to claim 25, wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery, subcutaneously, intraadiposally, intraarticularly, and intrathecally.

31. An article of manufacture comprising:
a compound of the formula



or stereoisomers or pharmaceutically acceptable salts thereof; and
packaging materials.

32. The article of manufacture of claim 31, wherein the packaging material comprises a container for housing the compound.

33. The article of manufacture of claim 32, wherein the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered wherein the disease state is diabetes, storage information, dosing information and/or instructions regarding how to administer the composition.

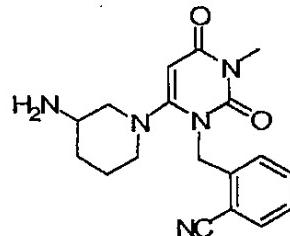
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,807,689 B2
APPLICATION NO. : 11/080992
DATED : October 5, 2010
INVENTOR(S) : Zhiyuan Zhang et al.

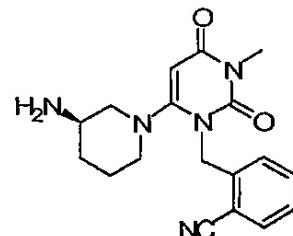
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Replace the structure:



in Column 81, Claim 4,
in Column 82, Claim 12,
in Column 83, Claim 19,
in Column 84, Claim 25, and
in Column 85, Claim 35 and Claim 39 with structure



Signed and Sealed this
Twentieth Day of March, 2012

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT 2

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Additional Information about Patents

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- Patent listings published prior to August 18, 2003, only identify method-of-use claims. The listed patents may include drug substance and/or drug product claims that are not indicated in the listing.
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not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N022271

Product 001

ALOGLIPTIN BENZOATE (NESINA) TABLET EQ 6.25MG BASE

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	6890898	02/02/2019			U-1335		
001	7078381	02/02/2019			U-1335		
001	7459428	02/02/2019			U-1336		
001	7807689	06/27/2028	DS	DP	U-1337		
001	8173663	12/02/2025			U-1338		01/19/2017
001	8288539	03/15/2025	DS				
001	8697125	06/16/2029		DP			05/27/2014

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
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Product No	Exclusivity Code	Exclusivity Expiration
001	M-177	04/05/2019

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EXHIBIT 3

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Patent and Exclusivity for: N203414

Product 001

ALOGLIPTIN BENZOATE; METFORMIN HYDROCHLORIDE (KAZANO) TABLET EQ 12.5MG BASE;500MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	6890898	02/02/2019			U-1335		
001	7078381	02/02/2019			U-1335		
001	7459428	02/02/2019			U-1336		
001	7807689	06/27/2028	DS	DP	U-1337		
001	8173663	03/15/2025			U-1338		
001	8288539	06/24/2025	DS				
001	8900638	05/24/2029		DP			12/18/2014

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
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Product No	Exclusivity Code	Exclusivity Expiration
001	M-177	04/05/2019

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EXHIBIT 4

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Patent and Exclusivity for: N022426

Product 004

ALOGLIPTIN BENZOATE; PIOGLITAZONE HYDROCHLORIDE (OSENI) TABLET EQ 12.5MG BASE;EQ 15MG BASE

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
004	6329404	06/19/2021		DP	U-1334		01/19/2017
004	6890898	02/02/2019			U-1335		
004	7078381	02/02/2019			U-1335		
004	7459428	02/02/2019			U-1336		
004	7807689	06/27/2028	DS	DP	U-1337		
004	8173663	03/15/2025			U-1338		
004	8288539	03/15/2025	DS				
004	8637079	06/04/2029		DP			02/13/2014

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
004	M-177	04/05/2019

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EXHIBIT 5

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NESINA safely and effectively. See full prescribing information for NESINA.

NESINA (alogliptin) tablets, for oral use

Initial U.S. Approval: 2013

INDICATIONS AND USAGE

NESINA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1, 14)

Important Limitations of Use: Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)

DOSAGE AND ADMINISTRATION

- The recommended dose in patients with normal renal function or mild renal impairment is 25 mg once daily. (2.1)
- Can be taken with or without food. (2.1)
- Adjust dose if moderate or severe renal impairment or end-stage renal disease (ESRD). (2.2)

Degree of Renal Impairment	Creatinine Clearance (mL/min)	Recommended Dosing
Moderate	≥30 to <60	12.5 mg once daily
Severe/ESRD	<30	6.25 mg once daily

DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg, 12.5 mg and 6.25 mg (3)

CONTRAINdications

History of a serious hypersensitivity reaction to alogliptin-containing products, such as anaphylaxis, angioedema or severe cutaneous adverse reactions. (4)

WARNINGS AND PRECAUTIONS

- Acute pancreatitis:** There have been postmarketing reports of acute pancreatitis. If pancreatitis is suspected, promptly discontinue NESINA. (5.1)
- Heart failure:** Consider the risks and benefits of NESINA prior to initiating treatment in patients at risk for heart failure. If heart

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE**
 - Monotherapy and Combination Therapy
- DOSAGE AND ADMINISTRATION**
 - Recommended Dosing
 - Patients with Renal Impairment
- DOSAGE FORMS AND STRENGTHS**
- CONTRAINDICATIONS**
- WARNINGS AND PRECAUTIONS**
 - Pancreatitis
 - Heart Failure
 - Hypersensitivity Reactions
 - Hepatic Effects
 - Use with Medications Known to Cause Hypoglycemia
 - Severe and Disabling Arthralgia
 - Bullous Pemphigoid
 - Macrovascular Outcomes
- ADVERSE REACTIONS**
 - Clinical Trials Experience
 - Postmarketing Experience
- DRUG INTERACTIONS**
- USE IN SPECIFIC POPULATIONS**
 - Pregnancy

failure develops, evaluate and manage according to current standards of care and consider discontinuation of NESINA (5.2).

- Hypersensitivity:** There have been postmarketing reports of serious hypersensitivity reactions in patients treated with NESINA such as anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. In such cases, promptly discontinue NESINA, assess for other potential causes, institute appropriate monitoring and treatment and initiate alternative treatment for diabetes. (5.3)
- Hepatic effects:** Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt NESINA and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart NESINA if liver injury is confirmed and no alternative etiology can be found. (5.4)
- Hypoglycemia:** When an insulin secretagogue (e.g., sulfonylurea) or insulin is used in combination with NESINA, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.5)
- Arthralgia:** Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.6)
- Bullous pemphigoid:** There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue NESINA. (5.7)
- Macrovascular outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with NESINA or any other antidiabetic drug. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (4% or greater incidence) are nasopharyngitis, headache and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2019

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*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

NESINA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see *Clinical Studies (14)*].

Important Limitations of Use

NESINA is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of NESINA is 25 mg once daily. NESINA may be taken with or without food.

2.2 Patients with Renal Impairment

No dose adjustment of NESINA is necessary for patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 mL/min).

The dose of NESINA is 12.5 mg once daily for patients with moderate renal impairment (CrCl ≥ 30 to < 60 mL/min).

The dose of NESINA is 6.25 mg once daily for patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min) or with end-stage renal disease (ESRD) (CrCl < 15 mL/min or requiring hemodialysis). NESINA may be administered without regard to the timing of dialysis. NESINA has not been studied in patients undergoing peritoneal dialysis [see *Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

Because there is a need for dose adjustment based upon renal function, assessment of renal function is recommended prior to initiation of NESINA therapy and periodically thereafter.

3 DOSAGE FORMS AND STRENGTHS

- 25 mg tablets are light red, oval, biconvex, film-coated, with “TAK ALG-25” printed on one side.
- 12.5 mg tablets are yellow, oval, biconvex, film-coated, with “TAK ALG-12.5” printed on one side.
- 6.25 mg tablets are light pink, oval, biconvex, film-coated, with “TAK ALG-6.25” printed on one side.

4 CONTRAINDICATIONS

History of a serious hypersensitivity reaction to alogliptin-containing products, such as anaphylaxis, angioedema or severe cutaneous adverse reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

Acute pancreatitis has been reported in the postmarketing setting and in randomized clinical trials. In glycemic control trials in patients with type 2 diabetes, acute pancreatitis was reported in 6 (0.2%) patients treated with NESINA 25 mg and 2 ($< 0.1\%$) patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and

high cardiovascular (CV) risk), acute pancreatitis was reported in 10 (0.4%) of patients treated with NESINA and in 7 (0.3%) of patients treated with placebo.

It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using NESINA.

After initiation of NESINA, patients should be observed for signs and symptoms of pancreatitis. If pancreatitis is suspected, NESINA should promptly be discontinued and appropriate management should be initiated.

5.2 Heart Failure

In the EXAMINE trial which enrolled patients with type 2 diabetes and recent acute coronary syndrome, 106 (3.9%) of patients treated with NESINA and 89 (3.3%) of patients treated with placebo were hospitalized for congestive heart failure.

Consider the risks and benefits of NESINA prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Patients should be advised of the characteristic symptoms of heart failure and should be instructed to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of NESINA.

5.3 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with NESINA. These reactions include anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. If a serious hypersensitivity reaction is suspected, discontinue NESINA, assess for other potential causes for the event and institute alternative treatment for diabetes [see *Adverse Reactions (6.2)*]. Use caution in patients with a history of angioedema with another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with NESINA.

5.4 Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking NESINA, although some of the reports contain insufficient information necessary to establish the probable cause [see *Adverse Reactions (6.2)*].

In glycemic control trials in patients with type 2 diabetes, serum alanine aminotransferase (ALT) elevations greater than three times the upper limit of normal (ULN) were reported in 1.3% of patients treated with NESINA 25 mg and 1.7% of patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), increases in serum alanine aminotransferase three times the upper limit of the reference range occurred in 2.4% of patients treated with NESINA and in 1.8% of patients treated with placebo.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have clinically significant liver enzyme elevations and if abnormal liver tests persist or worsen, NESINA should be interrupted and investigation done to establish the probable cause. NESINA should not be restarted in these patients without another explanation for the liver test abnormalities.

5.5 Use with Medications Known to Cause Hypoglycemia

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia.

Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with NESINA.

5.6 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.7 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving NESINA. If bullous pemphigoid is suspected, NESINA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.8 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with NESINA or any other antidiabetic drug.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Pancreatitis [see *Warnings and Precautions (5.1)*]
- Heart Failure [see *Warnings and Precautions (5.2)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.3)*]
- Hepatic Effects [see *Warnings and Precautions (5.4)*]
- Severe and Disabling Arthralgia [see *Warnings and Precautions (5.6)*]
- Bullous Pemphigoid [see *Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 14,778 patients with type 2 diabetes participated in 14 randomized, double-blind, controlled clinical trials of whom 9052 subjects were treated with NESINA, 3469 subjects were treated with placebo and 2257 were treated with an active comparator. The mean duration of diabetes was seven years, the mean body mass index (BMI) was 31 kg/m² (49% of patients had a BMI ≥30 kg/m²), and the mean age was 58 years (26% of patients ≥65 years of age). The mean exposure to NESINA was 49 weeks with 3348 subjects treated for more than one year.

In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse reactions was 73% in patients treated with NESINA 25 mg compared to 75% with placebo and 70% with active comparator. Overall discontinuation of therapy due to adverse reactions was 6.8% with NESINA 25 mg compared to 8.4% with placebo or 6.2% with active comparator.

Adverse reactions reported in ≥4% of patients treated with NESINA 25 mg and more frequently than in patients who received placebo are summarized in Table 1.

Table 1. Adverse Reactions Reported in ≥4% Patients Treated with NESINA 25 mg and More Frequently Than in Patients Given Placebo in Pooled Studies			
	Number of Patients (%)		
	NESINA 25 mg	Placebo	Active Comparator
	N=6447	N=3469	N=2257
Nasopharyngitis	309 (4.8)	152 (4.4)	113 (5.0)
Upper Respiratory Tract Infection	287 (4.5)	121 (3.5)	113 (5.0)
Headache	278 (4.3)	101 (2.9)	121 (5.4)

Hypoglycemia

Hypoglycemic events were documented based upon a blood glucose value and/or clinical signs and symptoms of hypoglycemia.

In the monotherapy study, the incidence of hypoglycemia was 1.5% in patients treated with NESINA compared to 1.6% with placebo. The use of NESINA as add-on therapy to glyburide or insulin did not increase the incidence of hypoglycemia compared to placebo. In a monotherapy study comparing NESINA to a sulfonylurea in elderly patients, the incidence of hypoglycemia was 5.4% with NESINA compared to 26% with glipizide (*Table 2*).

Table 2. Incidence and Rate of Hypoglycemia* in Placebo and Active-Controlled Studies when NESINA Was Used as Add-On Therapy to Glyburide, Insulin, Metformin, Pioglitazone or Compared to Glipizide or Metformin

Add-On to Glyburide (26 Weeks)	NESINA 25 mg	Placebo
	N=198	N=99
Overall (%)	19 (9.6)	11 (11.1)
Severe (%) [†]	0	1 (1)
Add-On to Insulin (\pm Metformin) (26 Weeks)	NESINA 25 mg	Placebo
	N=129	N=129
Overall (%)	35 (27)	31 (24)
Severe (%) [†]	1 (0.8)	2 (1.6)
Add-On to Metformin (26 Weeks)	NESINA 25 mg	Placebo
	N=207	N=104
Overall (%)	0	3 (2.9)
Severe (%) [†]	0	0
Add-On to Pioglitazone (\pm Metformin or Sulfonylurea) (26 Weeks)	NESINA 25 mg	Placebo
	N=199	N=97
Overall (%)	14 (7.0)	5 (5.2)
Severe (%) [†]	0	1 (1)
Compared to Glipizide (52 Weeks)	NESINA 25 mg	Glipizide
	N=222	N=219
Overall (%)	12 (5.4)	57 (26)
Severe (%) [†]	0	3 (1.4)
Compared to Metformin (26 Weeks)	NESINA 25 mg	Metformin 500 mg twice daily
	N=112	N=109
Overall (%)	2 (1.8)	2 (1.8)
Severe (%) [†]	0	0

Add-On to Metformin Compared to Glipizide (52 Weeks)	NESINA 25 mg	Glipizide
	N=877	N=869
Overall (%)	12 (1.4)	207 (23.8)
Severe (%) [†]	0	4 (0.5)

*Adverse reactions of hypoglycemia were based on all reports of symptomatic and asymptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.

[†]Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level or loss of consciousness or seizure.

In the EXAMINE trial, the incidence of investigator reported hypoglycemia was 6.7% in patients receiving NESINA and 6.5% in patients receiving placebo. Serious adverse reactions of hypoglycemia were reported in 0.8% of patients treated with NESINA and in 0.6% of patients treated with placebo.

Renal Impairment

In glycemic control trials in patients with type 2 diabetes, 3.4% of patients treated with NESINA and 1.3% of patients treated with placebo had renal function adverse reactions. The most commonly reported adverse reactions were renal impairment (0.5% for NESINA and 0.1% for active comparators or placebo), decreased creatinine clearance (1.6% for NESINA and 0.5% for active comparators or placebo) and increased blood creatinine (0.5% for NESINA and 0.3% for active comparators or placebo) [see *Use in Specific Populations (8.6)*].

In the EXAMINE trial of high CV risk type 2 diabetes patients, 23% of patients treated with NESINA and 21% of patients treated with placebo had an investigator reported renal impairment adverse reaction. The most commonly reported adverse reactions were renal impairment (7.7% for NESINA and 6.7% for placebo), decreased glomerular filtration rate (4.9% for NESINA and 4.3% for placebo) and decreased renal clearance (2.2% for NESINA and 1.8% for placebo). Laboratory measures of renal function were also assessed. Estimated glomerular filtration rate decreased by 25% or more in 21.1% of patients treated with NESINA and 18.7% of patients treated with placebo. Worsening of chronic kidney disease stage was seen in 16.8% of patients treated with NESINA and in 15.5% of patients treated with placebo.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the postmarketing use of NESINA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Acute pancreatitis, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and severe cutaneous adverse reactions, including Stevens-Johnson syndrome, hepatic enzyme elevations, fulminant hepatic failure, severe and disabling arthralgia, bullous pemphigoid, rhabdomyolysis, and diarrhea, constipation, nausea, and ileus [see *Warnings and Precautions (5.1, 5.3, 5.4, 5.6, 5.7)*].

7 DRUG INTERACTIONS

NESINA is primarily renally excreted. Cytochrome (CYP) P450-related metabolism is negligible. No significant drug-drug interactions were observed with the CYP-substrates or inhibitors tested or with renally excreted drugs [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with NESINA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

No adverse developmental effects were observed when alogliptin was administered to pregnant rats and rabbits during organogenesis at exposures 180- and 149-times the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC) [see *Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

Alogliptin administered to pregnant rabbits and rats during the period of organogenesis did not cause adverse developmental effects at doses of up to 200 mg/kg and 500 mg/kg, or 149 times and 180 times, the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC). Placental transfer of alogliptin into the fetus was observed following oral dosing to pregnant rats.

No adverse developmental outcomes were observed in offspring when alogliptin was administered to pregnant rats during gestation and lactation at doses up to 250 mg/kg (~ 95 times the 25 mg clinical dose, based on AUC).

8.2 Lactation

Risk Summary

There is no information regarding the presence of alogliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Alogliptin is present in rat milk; however, due to species specific differences in lactation physiology, animal lactation data may not reliably predict levels in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NESINA and any potential adverse effects on the breastfed infant from NESINA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of NESINA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients (N=9052) in clinical safety and efficacy studies treated with NESINA, 2257 (24.9%) patients were 65 years and older and 386 (4.3%) patients were 75 years and older. No overall differences in safety or effectiveness were observed between patients 65 years and over and

younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

A total of 602 patients with moderate renal impairment (eGFR ≥ 30 and < 60 mL/min/1.73 m²) and 4 patients with severe renal impairment/end-stage renal disease (eGFR < 30 mL/min/1.73 m² or < 15 mL/min/1.73 m², respectively) at baseline were treated with NESINA in clinical trials in patients with type 2 diabetes. Reductions in HbA1c were generally similar in this subgroup of patients. The overall incidence of adverse reactions was generally balanced between NESINA and placebo treatments in this subgroup of patients.

In the EXAMINE trial of high CV risk type 2 diabetes patients, 694 patients had moderate renal impairment and 78 patients had severe renal impairment or end-stage renal disease at baseline. The overall incidences of adverse reactions, serious adverse reactions and adverse reactions leading to study drug discontinuation were generally similar between the treatment groups.

8.7 Hepatic Impairment

No dose adjustments are required in patients with mild to moderate hepatic impairment (Child-Pugh Grade A and B) based on insignificant change in systemic exposures (e.g., AUC) compared to subjects with normal hepatic function in a pharmacokinetic study. NESINA has not been studied in patients with severe hepatic impairment (Child-Pugh Grade C). Use caution when administering NESINA to patients with liver disease [see *Warnings and Precautions* (5.3)].

10 OVERDOSAGE

The highest doses of NESINA administered in clinical trials were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes (equivalent to 32 times and 16 times the maximum recommended clinical dose of 25 mg, respectively). No serious adverse reactions were observed at these doses.

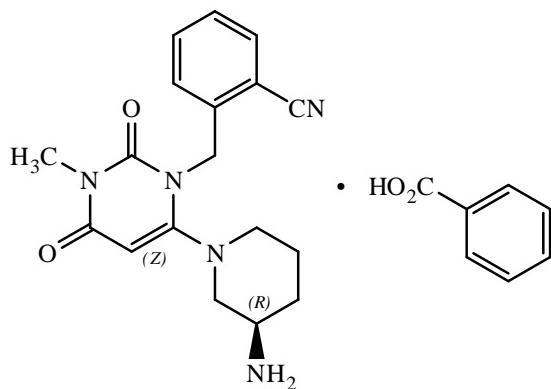
In the event of an overdose, it is reasonable to institute the necessary clinical monitoring and supportive therapy as dictated by the patient's clinical status. Per clinical judgment, it may be reasonable to initiate removal of unabsorbed material from the gastrointestinal tract.

Alogliptin is minimally dialyzable; over a three-hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to be beneficial in an overdose situation. It is not known if NESINA is dialyzable by peritoneal dialysis.

11 DESCRIPTION

NESINA tablets contain the active ingredient alogliptin, which is a selective, orally bioavailable inhibitor of the enzymatic activity of dipeptidyl peptidase-4 (DPP-4).

Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[{(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile monobenzoate. It has a molecular formula of C₁₈H₂₁N₅O₂•C₇H₆O₂ and a molecular weight of 461.51 daltons. The structural formula is:



Alogliptin benzoate is a white to off-white crystalline powder containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol and very slightly soluble in octanol and isopropyl acetate.

Each NESINA tablet contains 34 mg, 17 mg or 8.5 mg alogliptin benzoate, which is equivalent to 25 mg, 12.5 mg or 6.25 mg, respectively, of alogliptin and the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, ferric oxide (red or yellow) and polyethylene glycol, and is marked with printing ink (Gray F1).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

12.2 Pharmacodynamics

Single-dose administration of NESINA to healthy subjects resulted in a peak inhibition of DPP-4 within two to three hours after dosing. The peak inhibition of DPP-4 exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24 hours to active GLP-1 were three- to four-fold greater with NESINA (at doses of 25 to 200 mg) than placebo. In a 16-week, double-blind, placebo-controlled study, NESINA 25 mg demonstrated decreases in postprandial glucagon while increasing postprandial active GLP-1 levels compared to placebo over an eight-hour period following a standardized meal. It is unclear how these findings relate to changes in overall glycemic control in patients with type 2 diabetes mellitus. In this study, NESINA 25 mg demonstrated decreases in two-hour postprandial glucose compared to placebo (-30 mg/dL versus 17 mg/dL, respectively).

Multiple-dose administration of alogliptin to patients with type 2 diabetes also resulted in a peak inhibition of DPP-4 within one to two hours and exceeded 93% across all doses (25 mg, 100 mg and 400 mg) after a single dose and after 14 days of once-daily dosing. At these doses of NESINA, inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing.

Cardiac Electrophysiology

In a randomized, placebo-controlled, four-arm, parallel-group study, 257 subjects were administered either alogliptin 50 mg, alogliptin 400 mg, moxifloxacin 400 mg or placebo once daily for a total of seven days. No increase in corrected QT (QTc) was observed with either dose of alogliptin. At the 400 mg dose, peak alogliptin plasma concentrations were 19-fold higher than the peak concentrations following the maximum recommended clinical dose of 25 mg.

12.3 Pharmacokinetics

The pharmacokinetics of NESINA has been studied in healthy subjects and in patients with type 2 diabetes. After administration of single, oral doses up to 800 mg in healthy subjects, the peak plasma alogliptin concentration (median T_{max}) occurred one to two hours after dosing. At the maximum recommended clinical dose of 25 mg, NESINA was eliminated with a mean terminal half-life ($T_{1/2}$) of approximately 21 hours.

After multiple-dose administration up to 400 mg for 14 days in patients with type 2 diabetes, accumulation of alogliptin was minimal with an increase in total [e.g., area under the plasma concentration curve (AUC)] and peak (i.e., C_{max}) alogliptin exposures of 34% and 9%, respectively. Total and peak exposure to alogliptin increased proportionally across single doses and multiple doses of alogliptin ranging from 25 mg to 400 mg. The intersubject coefficient of variation for alogliptin AUC was 17%. The pharmacokinetics of NESINA was also shown to be similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of NESINA is approximately 100%. Administration of NESINA with a high-fat meal results in no significant change in total and peak exposure to alogliptin. NESINA may therefore be administered with or without food.

Distribution

Following a single, 12.5 mg intravenous infusion of alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L, indicating that the drug is well distributed into tissues.

Alogliptin is 20% bound to plasma proteins.

Metabolism

Alogliptin does not undergo extensive metabolism and 60% to 71% of the dose is excreted as unchanged drug in the urine.

Two minor metabolites were detected following administration of an oral dose of [^{14}C] alogliptin, *N*-demethylated, M-I (less than 1% of the parent compound), and *N*-acetylated alogliptin, M-II (less than 6% of the parent compound). M-I is an active metabolite and is an inhibitor of DPP-4 similar to the parent molecule; M-II does not display any inhibitory activity toward DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

Alogliptin exists predominantly as the (*R*)-enantiomer (more than 99%) and undergoes little or no chiral conversion *in vivo* to the (*S*)-enantiomer. The (*S*)-enantiomer is not detectable at the 25 mg dose.

Excretion

The primary route of elimination of [^{14}C] alogliptin-derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr.

Special Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of alogliptin 50 mg in patients with chronic renal impairment compared with healthy subjects.

In patients with mild renal impairment (creatinine clearance [CrCl] \geq 60 to <90 mL/min), an approximate 1.2-fold increase in plasma AUC of alogliptin was observed. Because increases of this magnitude are not considered clinically relevant, dose adjustment for patients with mild renal impairment is not recommended.

In patients with moderate renal impairment (CrCl \geq 30 to <60 mL/min), an approximate two-fold increase in plasma AUC of alogliptin was observed. To maintain similar systemic exposures of NESINA to those with normal renal function, the recommended dose is 12.5 mg once daily in patients with moderate renal impairment.

In patients with severe renal impairment (CrCl \geq 15 to <30 mL/min) and end-stage renal disease (ESRD) (CrCl <15 mL/min or requiring dialysis), an approximate three- and four-fold increase in plasma AUC of alogliptin were observed, respectively. Dialysis removed approximately 7% of the drug during a three-hour dialysis session. NESINA may be administered without regard to the timing of the dialysis. To maintain similar systemic exposures of NESINA to those with normal renal function, the recommended dose is 6.25 mg once daily in patients with severe renal impairment, as well as in patients with ESRD requiring dialysis.

Hepatic Impairment

Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment (Child-Pugh Grade B) compared to healthy subjects. The magnitude of these reductions is not considered to be clinically meaningful. Patients with severe hepatic impairment (Child-Pugh Grade C) have not been studied. Use caution when administering NESINA to patients with liver disease [see *Use in Specific Populations (8.6)* and *Warnings and Precautions (5.3)*].

Gender

No dose adjustment of NESINA is necessary based on gender. Gender did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Geriatric

No dose adjustment of NESINA is necessary based on age. Age did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Pediatric

Studies characterizing the pharmacokinetics of alogliptin in pediatric patients have not been performed.

Race

No dose adjustment of NESINA is necessary based on race. Race (White, Black, and Asian) did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Drug Interactions

In Vitro Assessment of Drug Interactions

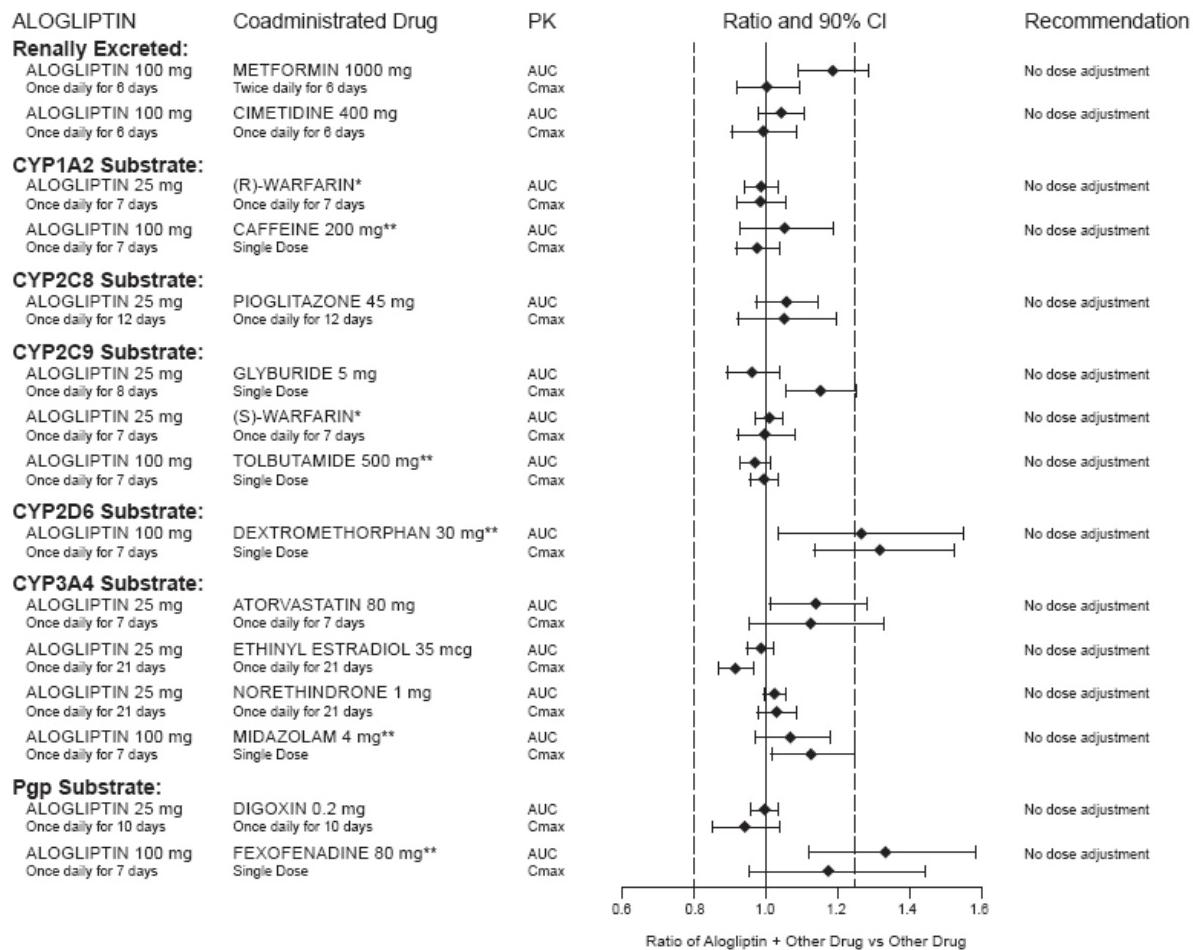
In vitro studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

Effects of Alogliptin on the Pharmacokinetics of Other Drugs

In clinical studies, alogliptin did not meaningfully increase the systemic exposure to the following drugs that are metabolized by CYP isozymes or excreted unchanged in urine (*Figure 1*). No dose adjustment of NESINA is recommended based on results of the described pharmacokinetic studies.

Figure 1. Effect of Alogliptin on the Pharmacokinetic Exposure to Other Drugs



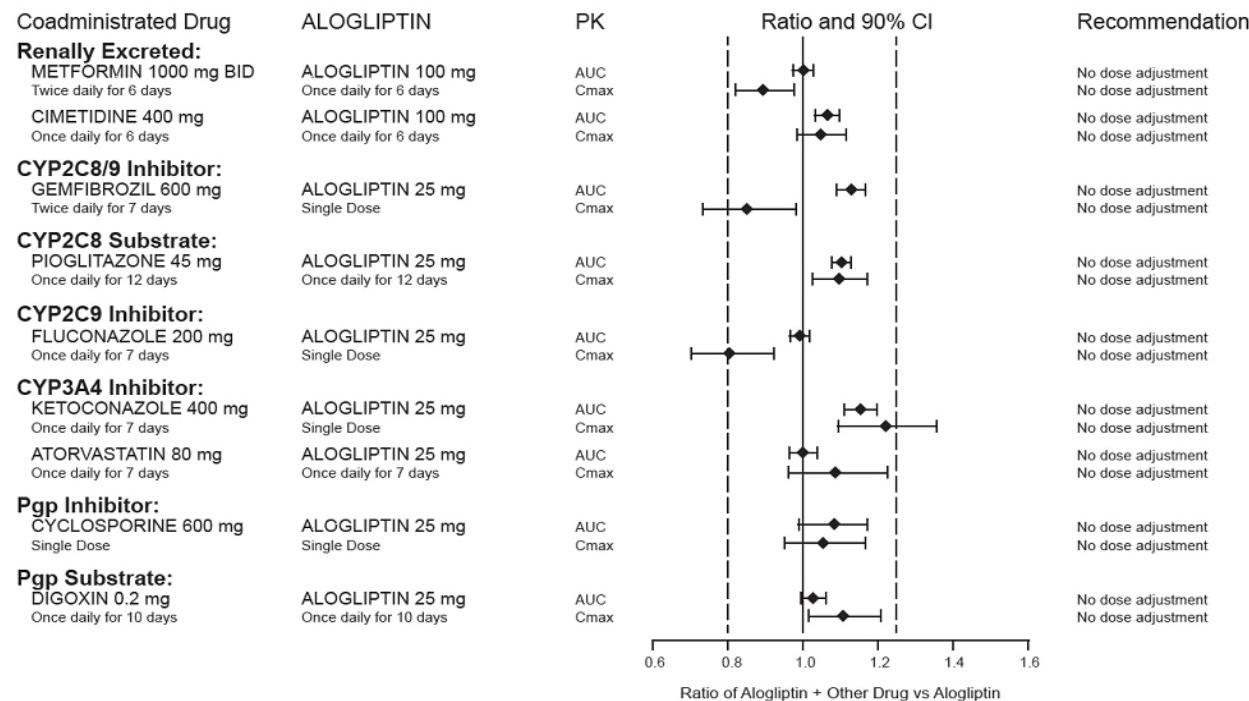
*Warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).

**Caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4 substrate) and fexofenadine (P-gp substrate) were administered as a cocktail.

Effects of Other Drugs on the Pharmacokinetics of Alogliptin

There are no clinically meaningful changes in the pharmacokinetics of alogliptin when NESINA is administered concomitantly with the drugs described below (*Figure 2*).

Figure 2. Effect of Other Drugs on the Pharmacokinetic Exposure of Alogliptin



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats were administered oral doses of 75, 400 and 800 mg/kg alogliptin for two years. No drug-related tumors were observed up to 75 mg/kg or approximately 32 times the maximum recommended clinical dose of 25 mg, based on area under the plasma concentration curve (AUC) exposure. At higher doses (approximately 308 times the maximum recommended clinical dose of 25 mg), a combination of thyroid C-cell adenomas and carcinomas increased in male but not female rats. No drug-related tumors were observed in mice after administration of 50, 150 or 300 mg/kg alogliptin for two years, or up to approximately 51 times the maximum recommended clinical dose of 25 mg, based on AUC exposure.

Alogliptin was not mutagenic or clastogenic, with and without metabolic activation, in the Ames test with *S. typhimurium* and *E. coli* or the cytogenetic assay in mouse lymphoma cells. Alogliptin was negative in the *in vivo* mouse micronucleus study.

In a fertility study in rats, alogliptin had no adverse effects on early embryonic development, mating or fertility at doses up to 500 mg/kg, or approximately 172 times the clinical dose based on plasma drug exposure (AUC).

14 CLINICAL STUDIES

NESINA has been studied as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione (either alone or in combination with metformin or a sulfonylurea) and insulin (either alone or in combination with metformin).

A total of 14,053 patients with type 2 diabetes were randomized in 11 double-blind, placebo- or active-controlled clinical safety and efficacy studies conducted to evaluate the effects of NESINA on glycemic control. The racial distribution of patients exposed to study medication was 70% Caucasian, 17% Asian, 6% Black and 7% other racial groups. The ethnic distribution was 30% Hispanic. Patients had an overall mean age of 57 years (range 21 to 91 years).

In patients with type 2 diabetes, treatment with NESINA produced clinically meaningful and statistically significant improvements in hemoglobin A1c (A1C) compared to placebo. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with NESINA appears to be related to the degree of A1C elevation at baseline.

NESINA had similar changes from baseline in serum lipids compared to placebo.

14.1 Patients with Inadequate Glycemic Control on Diet and Exercise

A total of 1768 patients with type 2 diabetes participated in three double-blind studies to evaluate the efficacy and safety of NESINA in patients with inadequate glycemic control on diet and exercise. All three studies had a four week, single-blind, placebo run-in period followed by a 26 week randomized treatment period. Patients who failed to meet prespecified hyperglycemic goals during the 26 week treatment periods received glycemic rescue therapy.

In a 26 week, double-blind, placebo-controlled study, a total of 329 patients (mean baseline A1C = 8%) were randomized to receive NESINA 12.5 mg, NESINA 25 mg or placebo once daily. Treatment with NESINA 25 mg resulted in statistically significant improvements from baseline in A1C and fasting plasma glucose (FPG) compared to placebo at Week 26 (*Table 3*). A total of 8% of patients receiving NESINA 25 mg and 30% of those receiving placebo required glycemic rescue therapy.

Improvements in A1C were not affected by gender, age or baseline body mass index (BMI).

The mean change in body weight with NESINA was similar to placebo.

Table 3. Glycemic Parameters at Week 26 in a Placebo-Controlled Monotherapy Study of NESINA*

	NEGINA 25 mg	Placebo
A1C (%)	N=128	N=63
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean [†])	-0.6	0
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-0.6 [‡] (-0.8, -0.3)	-
% of patients (n/N) achieving A1C ≤7%	44% (58/131) [‡]	23% (15/64)
FPG (mg/dL)	N=129	N=64
Baseline (mean)	172	173
Change from baseline (adjusted mean [†])	-16	11
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-28 [‡] (-40, -15)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region and duration of diabetes

[‡]p<0.01 compared to placebo

In a 26-week, double-blind, active-controlled study, a total of 655 patients (mean baseline A1C = 8.8%) were randomized to receive NESINA 25 mg alone, pioglitazone 30 mg alone, NESINA 12.5 mg with pioglitazone 30 mg or NESINA 25 mg with pioglitazone 30 mg once daily. Coadministration of NESINA 25 mg with pioglitazone 30 mg resulted in statistically significant improvements from baseline in A1C and FPG compared to NESINA 25 mg alone and to pioglitazone 30 mg alone (*Table 4*). A total of 3% of patients receiving NESINA 25 mg coadministered with pioglitazone 30 mg, 11% of those receiving NESINA 25 mg alone and 6% of those receiving pioglitazone 30 mg alone required glycemic rescue.

Improvements in A1C were not affected by gender, age or baseline BMI.

The mean increase in body weight was similar between pioglitazone alone and NESINA when coadministered with pioglitazone.

Table 4. Glycemic Parameters at Week 26 in an Active-Controlled Study of NESINA, Pioglitazone, and NESINA in Combination with Pioglitazone*

	NESINA 25 mg	Pioglitazone 30 mg	NESINA 25 mg + Pioglitazone 30 mg
A1C (%)	N=160	N=153	N=158
Baseline (mean)	8.8	8.8	8.8
Change from baseline (adjusted mean [†])	-1.0	-1.2	-1.7
Difference from NESINA 25 mg (adjusted mean [†] with 95% confidence interval)	-	-	-0.8 [‡] (-1.0, -0.5)
Difference from pioglitazone 30 mg (adjusted mean [†] with 95% confidence interval)	-	-	-0.6 [‡] (-0.8, -0.3)
% of patients (n/N) achieving A1C ≤7%	24% (40/164)	34% (55/163)	63% (103/164) [‡]
FPG (mg/dL)	N=162	N=157	N=162
Baseline (mean)	189	189	185
Change from baseline (adjusted mean [†])	-26	-37	-50
Difference from NESINA 25 mg (adjusted mean [†] with 95% confidence interval)	-	-	-24 [‡] (-34, -15)
Difference from pioglitazone 30 mg (adjusted mean [†] with 95% confidence interval)	-	-	-13 [‡] (-22, -4)

*Intent-to-treat population using last observation carried forward

[†]Least squares means adjusted for treatment, geographic region and baseline value

[‡]p<0.01 compared to NESINA 25 mg or pioglitazone 30 mg

In a 26 week, double-blind, placebo-controlled study, a total of 784 patients inadequately controlled on diet and exercise alone (mean baseline A1C = 8.4%) were randomized to one of seven treatment groups: placebo; metformin HCl 500 mg or metformin HCl 1000 mg twice daily; NESINA 12.5 mg twice daily; NESINA 25 mg daily; or NESINA 12.5 mg in combination with metformin HCl 500 mg or metformin HCl 1000 mg twice daily. Both coadministration treatment arms (NESINA 12.5 mg + metformin HCl 500 mg and NESINA 12.5 mg + metformin HCl 1000 mg) resulted in statistically significant improvements in A1C and FPG when compared with their respective individual alogliptin and metformin component regimens (*Table 5*). Coadministration treatment arms demonstrated improvements in two hour postprandial glucose (PPG) compared to NESINA alone or metformin alone (*Table 5*). A total of 12.3% of patients receiving NESINA 12.5 mg + metformin HCl 500 mg, 2.6% of patients receiving NESINA 12.5 mg + metformin HCl 1000 mg, 17.3% of patients receiving NESINA 12.5 mg, 22.9% of patients receiving metformin HCl 500 mg, 10.8% of patients receiving metformin HCl 1000 mg and 38.7% of patients receiving placebo required glycemic rescue.

Improvements in A1C were not affected by gender, age, race or baseline BMI. The mean decrease in body weight was similar between metformin alone and NESINA when coadministered with metformin.

Table 5. Glycemic Parameters at Week 26 for NESINA and Metformin Alone and in Combination in Patients with Type 2 Diabetes

	Placebo	NESINA 12.5 mg Twice Daily	Metformin HCl 500 mg Twice Daily	Metformin HCl 1000 mg Twice Daily	NESINA 12.5 mg + Metformin HCl 500 mg Twice Daily	NESINA 12.5 mg + Metformin HCl 1000 mg Twice Daily
A1C (%)*	N=102	N=104	N=103	N=108	N=102	N=111
Baseline (mean)	8.5	8.4	8.5	8.4	8.5	8.4
Change from baseline (adjusted mean [†])	0.1	-0.6	-0.7	-1.1	-1.2	-1.6
Difference from metformin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-0.6 [‡] (-0.9, -0.3)	-0.4 [‡] (-0.7, -0.2)
Difference from NESINA (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-0.7 [‡] (-1.0, -0.4)	-1.0 [‡] (-1.3, -0.7)
% of patients (n/N) achieving A1C <7% [§]	4% (4/102)	20% (21/104)	27% (28/103)	34% (37/108)	47% [‡] (48/102)	59% [‡] (66/111)
FPG (mg/dL)*	N=105	N=106	N=106	N=110	N=106	N=112
Baseline (mean)	187	177	180	181	176	185
Change from baseline (adjusted mean [†])	12	-10	-12	-32	-32	-46
Difference from metformin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-20 [‡] (-33, -8)	-14 [‡] (-26, -2)
Difference from NESINA (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-22 [‡] (-35, -10)	-36 [‡] (-49, -24)
2-Hour PPG (mg/dL)	N=26	N=34	N=28	N=37	N=31	N=37
Baseline (mean)	263	272	247	266	261	268
Change from baseline (adjusted mean [†])	-21	-43	-49	-54	-68	-86 [‡]

Difference from metformin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-19 (-49, 11)	-32 [‡] (-58, -5)
Difference from NESINA (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-25 (-53, -3)	-43 [‡] (-70, -16)

*Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue

[†]Least squares means adjusted for treatment, geographic region and baseline value

[‡]p<0.05 when compared to metformin and NESINA alone

[§]Compared using logistic regression

[¶] Intent-to-treat population using data available at Week 26

14.2 Combination Therapy

Add-On Therapy to Metformin

A total of 2081 patients with type 2 diabetes participated in two 26 week, double-blind, placebo-controlled studies to evaluate the efficacy and safety of NESINA as add-on therapy to metformin. In both studies, patients were inadequately controlled on metformin at a dose of at least 1500 mg per day or at the maximum tolerated dose. All patients entered a four week, single-blind placebo run-in period prior to randomization. Patients who failed to meet prespecified hyperglycemic goals during the 26 week treatment periods received glycemic rescue therapy.

In the first 26 week, placebo-controlled study, a total of 527 patients already on metformin (mean baseline A1C = 8%) were randomized to receive NESINA 12.5 mg, NESINA 25 mg or placebo. Patients were maintained on a stable dose of metformin (median dose = 1700 mg) during the treatment period. NESINA 25 mg in combination with metformin resulted in statistically significant improvements from baseline in A1C and FPG at Week 26, when compared to placebo (*Table 6*). A total of 8% of patients receiving NESINA 25 mg and 24% of patients receiving placebo required glycemic rescue.

Improvements in A1C were not affected by gender, age, baseline BMI or baseline metformin dose.

The mean decrease in body weight was similar between NESINA and placebo when given in combination with metformin.

Table 6. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of NESINA as Add-On Therapy to Metformin*

	NESINA 25 mg + Metformin	Placebo + Metformin
A1C (%)	N=203	N=103
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean [†])	-0.6	-0.1
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-0.5 [‡] (-0.7, -0.3)	-
% of patients (n/N) achieving A1C ≤7%	44% (92/207) [‡]	18% (19/104)
FPG (mg/dL)	N=204	N=104
Baseline (mean)	172	180
Change from baseline (adjusted mean [†])	-17	0
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-17 [‡] (-26, -9)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose

[‡]p<0.001 compared to placebo

In the second 26 week, double-blind, placebo-controlled study, a total of 1554 patients already on metformin (mean baseline A1C = 8.5%) were randomized to one of 12 double-blind treatment groups: placebo; 12.5 mg or 25 mg of NESINA alone; 15 mg, 30 mg or 45 mg of pioglitazone alone; or 12.5 mg or 25 mg of NESINA in combination with 15 mg, 30 mg or 45 mg of pioglitazone. Patients were maintained on a stable dose of metformin (median dose = 1700 mg) during the treatment period. Coadministration of NESINA and pioglitazone provided statistically significant improvements in A1C and FPG compared to placebo, to NESINA alone or to pioglitazone alone when added to background metformin therapy (*Table 7, Figure 3*). In addition, improvements from baseline A1C were comparable between NESINA alone and pioglitazone alone (15 mg, 30 mg and 45 mg) at Week 26. A total of 4%, 5% or 2% of patients receiving NESINA 25 mg with 15 mg, 30 mg or 45 mg pioglitazone, 33% of patients receiving placebo, 13% of patients receiving NESINA 25 mg and 10%, 15% or 9% of patients receiving pioglitazone 15 mg, 30 mg or 45 mg alone required glycemic rescue.

Improvements in A1C were not affected by gender, age or baseline BMI.

The mean increase in body weight was similar between pioglitazone alone and NESINA when coadministered with pioglitazone.

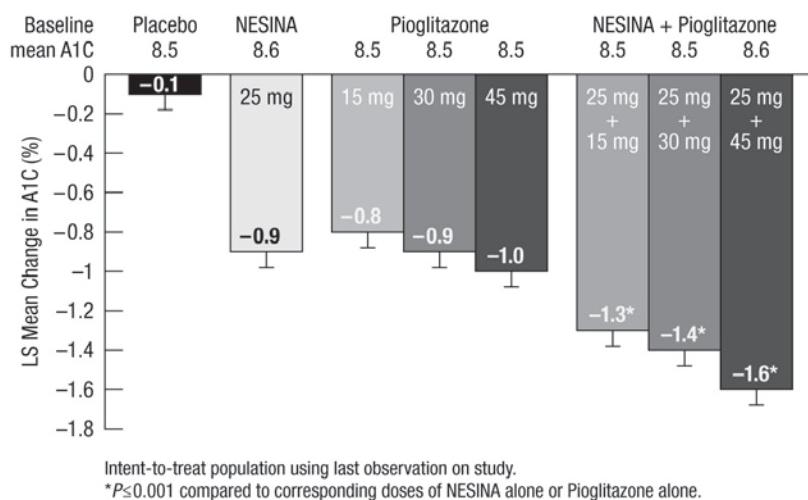
Table 7. Glycemic Parameters in a 26-Week Study of NESINA, Pioglitazone and NESINA in Combination with Pioglitazone when Added to Metformin*

	Placebo	NESINA 25 mg	Pioglitazone 15 mg	Pioglitazone 30 mg	Pioglitazone 45 mg	NESINA 25 mg + Pioglitazone 15 mg	NESINA 25 mg + Pioglitazone 30 mg	NESINA 25 mg + Pioglitazone 45 mg
A1C (%)	N=126	N=123	N=127	N=123	N=126	N=127	N=124	N=126
Baseline (mean)	8.5	8.6	8.5	8.5	8.5	8.5	8.5	8.6
Change from baseline (adjusted mean [†])	-0.1	-0.9	-0.8	-0.9	-1.0	-1.3 [‡]	-1.4 [‡]	-1.6 [‡]
Difference from pioglitazone (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-0.5 [‡] (-0.7, -0.3)	-0.5 [‡] (-0.7, -0.3)	-0.6 [‡] (-0.8, -0.4)
Difference from NESINA (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-0.4 [‡] (-0.6, -0.1)	-0.5 [‡] (-0.7, -0.3)	-0.7 [‡] (-0.9, -0.5)
Patients (%) achieving A1C ≤7%	6% (8/129)	27% (35/129)	26% (33/129)	30% (38/129)	36% (47/129)	55% (71/130) [‡]	53% (69/130) [‡]	60% (78/130) [‡]
FPG (mg/dL)	N=129	N=126	N=127	N=125	N=129	N=130	N=126	N=127
Baseline (mean)	177	184	177	175	181	179	179	178
Change from baseline (adjusted mean [†])	7	-19	-24	-29	-32	-38 [‡]	-42 [‡]	-53 [‡]
Difference from pioglitazone (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-14 [‡] (-24, -5)	-13 [‡] (-23, -3)	-20 [‡] (-30, -11)
Difference from NESINA (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-19 [‡] (-29, -10)	-23 [‡] (-33, -13)	-34 [‡] (-44, -24)

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, geographic region, metformin dose and baseline value[‡]p≤0.01 when compared to corresponding doses of pioglitazone and NESINA alone

Figure 3. Change from Baseline in A1C at Week 26 with NESINA and Pioglitazone Alone and NESINA in Combination with Pioglitazone When Added to Metformin



Add-On Therapy to a Thiazolidinedione

In a 26 week, placebo-controlled study, a total of 493 patients inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea (10 mg) (mean baseline A1C = 8%) were randomized to receive NESINA 12.5 mg, NESINA 25 mg or placebo. Patients were maintained on a stable dose of pioglitazone (median dose = 30 mg) during the treatment period; those who were also previously treated on metformin (median dose = 2000 mg) or sulfonylurea (median dose = 10 mg) prior to randomization were maintained on the combination therapy during the treatment period. All patients entered into a four-week, single-blind placebo run-in period prior to randomization. Patients who failed to meet prespecified hyperglycemic goals during the 26 week treatment period received glycemic rescue therapy.

The addition of NESINA 25 mg once daily to pioglitazone therapy resulted in statistically significant improvements from baseline in A1C and FPG at Week 26, compared to placebo (*Table 8*). A total of 9% of patients who were receiving NESINA 25 mg and 12% of patients receiving placebo required glycemic rescue.

Improvements in A1C were not affected by gender, age, baseline BMI or baseline pioglitazone dose.

Clinically meaningful reductions in A1C were observed with NESINA compared to placebo regardless of whether subjects were receiving concomitant metformin or sulfonylurea (-0.2% placebo versus -0.9% NESINA) therapy or pioglitazone alone (0% placebo versus -0.52% NESINA).

The mean increase in body weight was similar between NESINA and placebo when given in combination with pioglitazone.

Table 8. Glycemic Parameters in a 26 Week, Placebo-Controlled Study of NESINA as Add-On Therapy to Pioglitazone*

	NESINA 25 mg + Pioglitazone ± Metformin ± Sulfonylurea	Placebo + Pioglitazone ± Metformin ± Sulfonylurea
A1C (%)	N=195	N=95
Baseline (mean)	8	8
Change from baseline (adjusted mean [†])	-0.8	-0.2
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-0.6 [‡] (-0.8, -0.4)	-
% of patients (n/N) achieving A1C ≤7%	49% (98/199) [‡]	34% (33/97)
FPG (mg/dL)	N=197	N=97
Baseline (mean)	170	172
Change from baseline (adjusted mean [†])	-20	-6
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-14 [‡] (-23, -5)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region, baseline treatment regimen (pioglitazone, pioglitazone + metformin or pioglitazone + sulfonylurea) and baseline pioglitazone dose

[‡]p<0.01 compared to placebo

Add-on Combination Therapy with Pioglitazone and Metformin

In a 52 week, active-comparator study, a total of 803 patients inadequately controlled (mean baseline A1C = 8.2%) on a current regimen of pioglitazone 30 mg and metformin at least 1500 mg per day or at the maximum tolerated dose were randomized to either receive the addition of NESINA 25 mg or the titration of pioglitazone 30 mg to 45 mg following a four-week, single-blind placebo run-in period. Patients were maintained on a stable dose of metformin (median dose = 1700 mg). Patients who failed to meet prespecified hyperglycemic goals during the 52 week treatment period received glycemic rescue therapy.

In combination with pioglitazone and metformin, NESINA 25 mg was shown to be statistically superior in lowering A1C and FPG compared with the titration of pioglitazone from 30 mg to 45 mg at Week 26 and at Week 52 (*Table 9; results shown only for Week 52*). A total of 11% of patients in the NESINA 25 mg treatment group and 22% of patients in the pioglitazone up-titration group required glycemic rescue.

Improvements in A1C were not affected by gender, age, race or baseline BMI.

The mean increase in body weight was similar in both treatment arms.

Table 9. Glycemic Parameters in a 52 Week, Active-Controlled Study of NESINA as Add-On Combination Therapy to Metformin and Pioglitazone*

	NESINA 25 mg + Pioglitazone 30 mg + Metformin	Pioglitazone 45 mg + Metformin
A1C (%)	N=397	N=394
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean [†])	-0.7	-0.3
Difference from pioglitazone 45 mg + metformin (adjusted mean [†] with 95% confidence interval)	-0.4 [‡] (-0.5, -0.3)	-
% of patients (n/N) achieving A1C≤7%	33% (134/404) [§]	21% (85/399)
Fasting Plasma Glucose (mg/dL)[‡]	N=399	N=396
Baseline (mean)	162	162
Change from baseline (adjusted mean [†])	-15	-4
Difference from pioglitazone 45 mg + metformin (adjusted mean [†] with 95% confidence interval)	-11 [§] (-16, -6)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose.

[‡]Noninferior and statistically superior to metformin + pioglitazone at the 0.025 one-sided significance level

[§]p<0.001 compared to pioglitazone 45 mg + metformin

Add-On Therapy to a Sulfonylurea

In a 26 week, placebo-controlled study, a total of 500 patients inadequately controlled on a sulfonylurea (mean baseline A1C = 8.1%) were randomized to receive NESINA 12.5 mg, NESINA 25 mg or placebo. Patients were maintained on a stable dose of glyburide (median dose = 10 mg) during the treatment period. All patients entered into a four week, single-blind, placebo run-in period prior to randomization. Patients who failed to meet prespecified hyperglycemic goals during the 26 week treatment period received glycemic rescue therapy.

The addition of NESINA 25 mg to glyburide therapy resulted in statistically significant improvements from baseline in A1C at Week 26 when compared to placebo (*Table 10*). Improvements in FPG observed with NESINA 25 mg were not statistically significant compared with placebo. A total of 16% of patients receiving NESINA 25 mg and 28% of those receiving placebo required glycemic rescue.

Improvements in A1C were not affected by gender, age, baseline BMI or baseline glyburide dose.

The mean change in body weight was similar between NESINA and placebo when given in combination with glyburide.

Table 10. Glycemic Parameters in a 26 Week, Placebo-Controlled Study of NESINA as Add-On Therapy to Glyburide*

	NESINA 25 mg + Glyburide	Placebo + Glyburide
A1C (%)	N=197	N=97
Baseline (mean)	8.1	8.2
Change from baseline (adjusted mean [†])	-0.5	0
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-0.5 [‡] (-0.7, -0.3)	-
% of patients (n/N) achieving A1C ≤7%	35% (69/198) [‡]	18% (18/99)
FPG (mg/dL)	N=198	N=99
Baseline (mean)	174	177
Change from baseline (adjusted mean [†])	-8	2
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-11 (-22, 1)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region and baseline glyburide dose[‡]p<0.01 compared to placebo

Add-On Therapy to Insulin

In a 26 week, placebo-controlled study, a total of 390 patients inadequately controlled on insulin alone (42%) or in combination with metformin (58%) (mean baseline A1C = 9.3%) were randomized to receive NESINA 12.5 mg, NESINA 25 mg or placebo. Patients were maintained on their insulin regimen (median dose = 55 IU) upon randomization and those previously treated with insulin in combination with metformin (median dose = 1700 mg) prior to randomization continued on the combination regimen during the treatment period. Patients entered the trial on short-, intermediate- or long-acting (basal) insulin or premixed insulin. Patients who failed to meet prespecified hyperglycemic goals during the 26 week treatment period received glycemic rescue therapy.

The addition of NESINA 25 mg once daily to insulin therapy resulted in statistically significant improvements from baseline in A1C and FPG at Week 26, when compared to placebo (*Table 11*). A total of 20% of patients receiving NESINA 25 mg and 40% of those receiving placebo required glycemic rescue.

Improvements in A1C were not affected by gender, age, baseline BMI or baseline insulin dose. Clinically meaningful reductions in A1C were observed with NESINA compared to placebo regardless of whether subjects were receiving concomitant metformin and insulin (-0.2% placebo versus -0.8% NESINA) therapy or insulin alone (0.1% placebo versus -0.7% NESINA).

The mean increase in body weight was similar between NESINA and placebo when given in combination with insulin.

Table 11. Glycemic Parameters in a 26-Week, Placebo-Controlled Study of NESINA as Add-On Therapy to Insulin*

	NESINA 25 mg + Insulin ± Metformin	Placebo + Insulin ± Metformin
A1C (%)	N=126	N=126
Baseline (mean)	9.3	9.3
Change from baseline (adjusted mean [†])	-0.7	-0.1
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-0.6 [‡] (-0.8, -0.4)	-
% of patients (n/N) achieving A1C ≤7%	8% (10/129)	1% (1/129)
FPG (mg/dL)	N=128	N=127
Baseline (mean)	186	196
Change from baseline (adjusted mean [†])	-12	6
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-18 [‡] (-33, -2)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region, baseline treatment regimen (insulin or insulin + metformin) and baseline daily insulin dose

[‡]p<0.05 compared to placebo

14.3 Cardiovascular Safety Trial

A randomized, double-blind, placebo-controlled cardiovascular outcomes trial (EXAMINE) was conducted to evaluate the cardiovascular risk of NESINA. The trial compared the risk of major adverse cardiovascular events (MACE) between NESINA (N=2701) and placebo (N=2679) when added to standard of care therapies for diabetes and atherosclerotic vascular disease (ASCVD). The trial was event driven and patients were followed until a sufficient number of primary outcome events accrued.

Eligible patients were adults with type 2 diabetes who had inadequate glycemic control at baseline (e.g., HbA1c >6.5%) and had been hospitalized for an acute coronary syndrome event (e.g., acute myocardial infarction or unstable angina requiring hospitalization) 15 to 90 days prior to randomization. The dose of NESINA was based on estimated renal function at baseline per dosage and administration recommendations [see *Dosage and Administration (2.2)*]. The average time between an acute coronary syndrome event and randomization was approximately 48 days.

The mean age of the population was 61 years. Most patients were male (68%), Caucasian (73%), and were recruited from outside of the United States (86%). Asian and Black patients contributed 20% and 4% of the total population, respectively. At the time of randomization patients had a

diagnosis of type 2 diabetes mellitus for approximately 9 years, 87% had a prior myocardial infarction and 14% were current smokers. Hypertension (83%) and renal impairment (27% with an eGFR ≤60 ml/min/1.73 m²) were prevalent co-morbid conditions. Use of medications to treat diabetes (e.g., metformin 73%, sulfonylurea 54%, insulin 41%), and ASCVD (e.g., statin 94%, aspirin 93%, renin-angiotensin system blocker 88%, beta-blocker 87%) was similar between patients randomized to NESINA and placebo at baseline. During the trial, medications to treat diabetes and ASCVD could be adjusted to ensure care for these conditions adhered to standard of care recommendations set by local practice guidelines.

The primary endpoint in EXAMINE was the time to first occurrence of a MACE defined as the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. The study was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE. The median exposure to study drug was 526 days and 95% of the patients were followed to study completion or death.

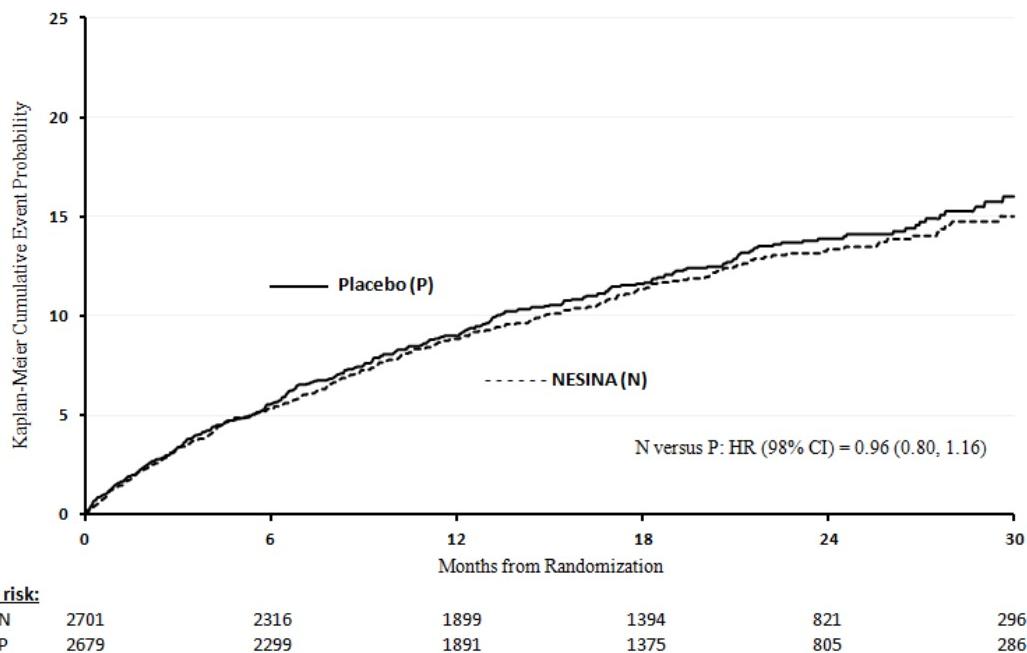
Table 12 shows the study results for the primary MACE composite endpoint and the contribution of each component to the primary MACE endpoint. The upper bound of the confidence interval was 1.16 and excluded a risk margin larger than 1.3.

Table 12. Patients with MACE in EXAMINE

Composite of first event of CV death, nonfatal MI or nonfatal stroke (MACE)	NESINA		Placebo		Hazard Ratio
	Number of Patients (%)	Rate per 100 PY*	Number of Patients (%)	Rate per 100 PY*	(98% CI)
	N=2701		N=2679		
CV Death	89 (3.3)	2.2	111 (4.1)	2.8	
Non-fatal MI	187 (6.9)	4.6	173 (6.5)	4.3	
Non-fatal stroke	29 (1.1)	0.7	32 (1.2)	0.8	

*Patient Years (PY)

The Kaplan-Meier based cumulative event probability is presented in Figure 4 for the time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for placebo and NESINA overlap throughout the duration of the study. The observed incidence of MACE was highest within the first 60 days after randomization in both treatment arms (14.8 MACE per 100 PY), decreased from day 60 to the end of the first year (8.4 per 100 PY) and was lowest after one year of follow-up (5.2 per 100 PY).

Figure 4. Observed Cumulative Rate of MACE in EXAMINE

The rate of all cause death was similar between treatment arms with 153 (3.6 per 100 PY) recorded among patients randomized to NESINA and 173 (4.1 per 100 PY) among patients randomized to placebo. A total of 112 deaths (2.9 per 100 PY) among patients on NESINA and 130 among patients on placebo (3.5 per 100 PY) were adjudicated as cardiovascular deaths.

16 HOW SUPPLIED/STORAGE AND HANDLING

NESINA tablets are available as film-coated tablets containing 25 mg, 12.5 mg or 6.25 mg of alogliptin as follows:

25 mg tablet: light red, oval, biconvex, film-coated, with "TAK ALG-25" printed on one side, available in:

NDC 64764-250-30	Bottles of 30 tablets
NDC 64764-250-90	Bottles of 90 tablets
NDC 64764-250-50	Bottles of 500 tablets

12.5 mg tablet: yellow, oval, biconvex, film-coated, with "TAK ALG-12.5" printed on one side, available in:

NDC 64764-125-30	Bottles of 30 tablets
NDC 64764-125-90	Bottles of 90 tablets
NDC 64764-125-50	Bottles of 500 tablets

6.25 mg tablet: light pink, oval, biconvex, film-coated, with "TAK ALG-6.25" printed on one side, available in:

NDC 64764-625-30	Bottles of 30 tablets
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NDC 64764-625-90 Bottles of 90 tablets

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the potential risks and benefits of NESINA.

Patients should be informed that acute pancreatitis has been reported during use of NESINA.

Patients should be informed that persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis.

Patients should be instructed to promptly discontinue NESINA and contact their physician if persistent severe abdominal pain occurs.

Patients should be informed of the signs and symptoms of heart failure. Before initiating NESINA, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Patients should be instructed to contact their healthcare providers as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight, or swelling of the feet.

Patients should be informed that allergic reactions have been reported during use of NESINA. If symptoms of allergic reactions (including skin rash, hives and swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing) occur, patients should be instructed to discontinue NESINA and seek medical advice promptly.

Patients should be informed that postmarketing reports of liver injury, sometimes fatal, have been reported during use of NESINA. If signs or symptoms of liver injury occur, patients should be instructed to discontinue NESINA and seek medical advice promptly.

Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue or insulin is used in combination with NESINA. Explain the risks, symptoms and appropriate management of hypoglycemia.

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [see *Warnings and Precautions (5.7)*].

Instruct patients to take NESINA only as prescribed. If a dose is missed, advise patients not to double their next dose.

Instruct patients to read the Medication Guide before starting NESINA therapy and to reread each time the prescription is refilled. Instruct patients to inform their healthcare provider if an unusual symptom develops or if a symptom persists or worsens.

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**MEDICATION GUIDE
NESINA (nes-see'-na)
(alogliptin)
tablets**

Read this Medication Guide carefully before you start taking NESINA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about NESINA, ask your doctor or pharmacist.

What is the most important information I should know about NESINA?

Serious side effects can happen to people taking NESINA, including:

1. **Inflammation of the pancreas (pancreatitis):** NESINA may cause pancreatitis which may be severe.

Certain medical conditions make you more likely to get pancreatitis.

Before you start taking NESINA:

Tell your doctor if you have ever had:

- pancreatitis
- kidney problems
- liver problems

Stop taking NESINA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

2. **Heart failure:**

Before you start taking NESINA:

Tell your healthcare provider if you have ever had heart failure or have problems with your kidneys.

Contact your healthcare provider right away if you have any of the following symptoms:

- increasing shortness of breath or trouble breathing especially when lying down
- an unusually fast increase in weight
- swelling of feet, ankles, or legs

These may be symptoms of heart failure.

What is NESINA?

- NESINA is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- NESINA is unlikely by itself to cause your blood sugar to be lowered to a dangerous level (hypoglycemia). However, hypoglycemia may still occur with NESINA.
- NESINA is not for people with type 1 diabetes.
- NESINA is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if NESINA is safe and effective in children under the age of 18.

Who should not take NESINA?

Do not take NESINA if you:

- Are allergic to any ingredients in NESINA or have had a serious allergic (hypersensitivity) reaction to NESINA. See the end of this Medication Guide for a complete list of the ingredients in NESINA.

Symptoms of a serious allergic reaction to NESINA may include:

- | | |
|--|---|
| <ul style="list-style-type: none"> ○ swelling of your face, lips, throat and other areas on your skin ○ raised, red areas on your skin (hives) | <ul style="list-style-type: none"> ○ difficulty with swallowing or breathing ○ skin rash, itching, flaking or peeling |
|--|---|

If you have any of these symptoms, stop taking NESINA and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before and during treatment with NESINA?

Before you take NESINA, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis)
- have kidney or liver problems
- have other medical conditions

- are pregnant or plan to become pregnant. It is not known if NESINA can harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant
- are breastfeeding or plan to breastfeed. It is not known whether NESINA passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking NESINA

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist before you start any new medicine.

NESINA may affect the way other medicines work, and other medicines may affect how NESINA works. Contact your doctor before you start or stop other types of medicines.

How should I take NESINA?

- Take NESINA exactly as your doctor tells you to take it.
- Take NESINA 1 time each day with or without food.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose, and take the next dose at your regular time. **Do not** take 2 doses of NESINA at the same time.
- If you take too much NESINA, call your doctor or go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start NESINA and during treatment as needed. Your doctor may change your dose of NESINA based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of NESINA?

NESINA can cause serious side effects, including:

See “**What is the most important information I should know about NESINA?**”

- **Allergic (hypersensitivity) reactions** such as:

- | | |
|--|--|
| <ul style="list-style-type: none"> ○ swelling of your face, lips, throat and other areas on your skin ○ raised, red areas on your skin (hives) | <ul style="list-style-type: none"> ○ difficulty swallowing or breathing ○ skin rash, itching, flaking or peeling |
|--|--|

If you have these symptoms, stop taking NESINA and contact your doctor right away.

- **Liver problems.** Call your doctor right away if you have unexplained symptoms, such as:

- | | | |
|--|--|---|
| <ul style="list-style-type: none"> ○ nausea or vomiting ○ loss of appetite | <ul style="list-style-type: none"> ○ stomach pain ○ dark urine | <ul style="list-style-type: none"> ○ unusual or unexplained tiredness ○ yellowing of your skin or the whites of your eyes |
|--|--|---|

- **Low blood sugar (hypoglycemia).** If you take NESINA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take NESINA. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your doctor. Signs and symptoms of low blood sugar include:

- | | | | | |
|--|--|---|---|--|
| <ul style="list-style-type: none"> ○ shaking or feeling jittery ○ fast heartbeat | <ul style="list-style-type: none"> ○ sweating ○ change in vision | <ul style="list-style-type: none"> ○ hunger ○ confusion | <ul style="list-style-type: none"> ○ headache ○ dizziness | <ul style="list-style-type: none"> ○ change in mood |
|--|--|---|---|--|

- **Joint pain.** Some people who take medicines called DPP-4 inhibitors like NESINA, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.

- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, like NESINA, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking NESINA.

The most common side effects of NESINA include stuffy or runny nose and sore throat, headache, or cold-like symptoms (upper respiratory tract infection).

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of NESINA. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NESINA?

Store NESINA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep NESINA and all medicines out of the reach of children.

General information about the safe and effective use of NESINA.

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take NESINA for a condition for which it was not prescribed. Do not give NESINA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about NESINA. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about NESINA that is written for health professionals.

For more information go to www.NESINA.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in NESINA?

Active ingredient: alogliptin

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate. In addition, the film-coating contains the following inactive ingredients: hypromellose, titanium dioxide, ferric oxide (red or yellow) and polyethylene glycol and is marked with gray F1 printing ink

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

12/2016

EXHIBIT 6

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KAZANO safely and effectively. See full prescribing information for KAZANO.

KAZANO (alogliptin and metformin HCl) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: LACTIC ACIDOSIS

- See full prescribing information for complete boxed warning.
- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradycardias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. (5.1)
 - Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)
 - If lactic acidosis is suspected, discontinue KAZANO and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

INDICATIONS AND USAGE

KAZANO is a dipeptidyl-peptidase-4 (DPP-4) inhibitor and a biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

Important Limitations of Use: Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Give twice daily with food. (2.1)
- Adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl. (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
 - Do not use in patients with eGFR below 60 mL/min/1.73 m². (2.2)
- KAZANO may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 12.5 mg alogliptin and 500 mg metformin HCl, 12.5 mg alogliptin and 1000 mg metformin HCl. (3)

CONTRAINDICATIONS

- Severe renal impairment: eGFR below 30 mL/min/1.73 m². (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4)
- History of a serious hypersensitivity reaction to alogliptin or metformin, components of KAZANO, such as anaphylaxis, angioedema or severe cutaneous adverse reactions. (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis: See boxed warning. (5.1)
- Acute pancreatitis: There have been postmarketing reports of acute pancreatitis. If pancreatitis is suspected, promptly discontinue KAZANO. (5.2)

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING: LACTIC ACIDOSIS****1 INDICATIONS AND USAGE**

1.1 Monotherapy and Combination Therapy

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

2.2 Recommendations for Use in Renal Impairment

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

- Heart failure: Consider the risks and benefits of KAZANO prior to initiating treatment in patients at risk for heart failure. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of KAZANO (5.3).
- Hypersensitivity: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin such as anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. In such cases, promptly discontinue KAZANO, assess for other potential causes, institute appropriate monitoring and treatment and initiate alternative treatment for diabetes. (5.4)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt KAZANO and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart KAZANO if liver injury is confirmed and no alternative etiology can be found. (5.5)
- Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. Monitor hematologic parameters annually. (5.6)
- Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. (5.7)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.8)
- Bullous pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue KAZANO. (5.9)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KAZANO or any other antidiabetic drug. (5.10)

ADVERSE REACTIONS

The most common adverse reactions (4% or greater incidence) are upper respiratory tract infection, nasopharyngitis, diarrhea, hypertension, headache, back pain and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.1)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine), may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.3)

USE IN SPECIFIC POPULATIONS

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Pediatrics: Safety and effectiveness of KAZANO in patients below the age of 18 have not been established. (8.4)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2019

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL [see *Warnings and Precautions (5.1)*].

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information [see *Dosage and Administration (2.2)*, *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Drug Interactions (7)*, and *Use in Specific Populations (8.6, 8.7)*].

If metformin-associated lactic acidosis is suspected, immediately discontinue KAZANO and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

KAZANO is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and metformin is appropriate [see *Clinical Studies (14)*].

Important Limitations of Use

KAZANO is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

- Healthcare providers should individualize the starting dose of KAZANO based on the patient's current regimen.
- KAZANO should be taken twice daily with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin. KAZANO tablets must not be split before swallowing.
- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl.

- The following doses are available:
 - 12.5 mg alogliptin and 500 mg metformin HCl
 - 12.5 mg alogliptin and 1000 mg metformin HCl

2.2 Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of KAZANO and periodically thereafter.

KAZANO is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

KAZANO is not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m² because these patients require a lower daily dosage of alogliptin than what is available in the fixed combination KAZANO product.

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue KAZANO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart KAZANO if renal function is stable [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- 12.5 mg/500 mg tablets are pale yellow, oblong, film-coated tablets with “12.5/500” debossed on one side and “322M” debossed on the other side
- 12.5 mg/1000 mg tablets are pale yellow, oblong, film-coated tablets with “12.5/1000” debossed on one side and “322M” debossed on the other side

4 CONTRAINDICATIONS

KAZANO is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²) [see *Warnings and Precautions (5.1)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to alogliptin or metformin, components of KAZANO, such as anaphylaxis, angioedema or severe cutaneous adverse reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradycardias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally greater than 5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be

instituted promptly in a hospital setting, along with immediate discontinuation of KAZANO. In KAZANO-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue KAZANO and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment

The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [see *Dosage and Administration* (2.2), *Clinical Pharmacology* (12.3)]:

- Before initiating KAZANO, obtain an eGFR.
- KAZANO is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see *Contraindications* (4)].
- KAZANO is not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m² because these patients require a lower dosage of alogliptin than what is available in the fixed combination KAZANO product.
- Obtain an eGFR at least annually in all patients taking KAZANO. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions

The concomitant use of KAZANO with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation [see *Drug Interactions* (7)]. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater

The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see *Use in Specific Populations* (8.5)].

Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop KAZANO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart KAZANO if renal function is stable.

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume

depletion, hypotension and renal impairment. KAZANO should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue KAZANO.

Excessive Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving KAZANO.

Hepatic Impairment

Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of KAZANO in patients with clinical or laboratory evidence of hepatic disease.

5.2 Pancreatitis

Acute pancreatitis has been reported in the postmarketing setting and in randomized clinical trials. In glycemic control trials in patients with type 2 diabetes, acute pancreatitis was reported in 6 (0.2%) patients treated with alogliptin 25 mg and 2 (<0.1%) patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), acute pancreatitis was reported in 10 (0.4%) patients treated with alogliptin and in 7 (0.3%) patients treated with placebo.

It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using KAZANO.

After initiation of KAZANO, patients should be observed for signs and symptoms of pancreatitis. If pancreatitis is suspected, alogliptin should promptly be discontinued and appropriate management should be initiated.

5.3 Heart Failure

In the EXAMINE trial which enrolled patients with type 2 diabetes and recent acute coronary syndrome, 106 (3.9%) of patients treated with alogliptin and 89 (3.3%) of patients treated with placebo were hospitalized for congestive heart failure.

Consider the risks and benefits of KAZANO prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Patients should be advised of the characteristic symptoms of heart failure and should be instructed to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of KAZANO.

5.4 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin. These reactions include anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. If a serious hypersensitivity reaction is suspected, discontinue KAZANO, assess for other potential causes for the event and institute alternative treatment for diabetes [see *Adverse Reactions (6.3)*]. Use caution in patients with a history of

angioedema with another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with KAZANO.

5.5 Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking alogliptin, although some of the reports contain insufficient information necessary to establish the probable cause [see *Adverse Reactions* (6.3)].

In glycemic control trials in patients with type 2 diabetes, serum alanine aminotransferase (ALT) elevations greater than three times the upper limit of normal (ULN) were reported in 1.3% of patients treated with alogliptin 25 mg and 1.7% of patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), increases in serum alanine aminotransferase three times the upper limit of the reference range occurred in 2.4% of patients treated with alogliptin and in 1.8% of patients treated with placebo.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have clinically significant liver enzyme elevations and if abnormal liver tests persist or worsen, KAZANO should be interrupted and investigation done to establish the probable cause. KAZANO should not be restarted in these patients without another explanation for the liver test abnormalities.

5.6 Vitamin B₁₂ Levels

In controlled, 29-week clinical trials of immediate-release metformin, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on KAZANO, and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurements at two- to three-year intervals may be useful.

5.7 Use with Medications Known to Cause Hypoglycemia

Alogliptin

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with KAZANO.

Metformin Hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking β-adrenergic blocking drugs.

5.8 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to

years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.9 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving KAZANO. If bullous pemphigoid is suspected, KAZANO should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.10 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KAZANO or any other antidiabetic drug.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Pancreatitis [see *Warnings and Precautions (5.2)*]
- Heart Failure [see *Warnings and Precautions (5.3)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.4)*]
- Hepatic Effects [see *Warnings and Precautions (5.5)*]
- Severe and Disabling Arthralgia [see *Warnings and Precautions (5.8)*]
- Bullous Pemphigoid [see *Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Alogliptin and Metformin Hydrochloride

Over 2700 patients with type 2 diabetes have received alogliptin coadministered with metformin in four large, randomized, double-blind controlled clinical trials. The mean exposure to KAZANO was 58 weeks, with more than 1400 subjects treated for more than one year. These included two 26 week placebo-controlled studies, one 52 week active control study and an interim analysis of a 104 week active-controlled study. In the KAZANO arm, the mean duration of diabetes was approximately six years, the mean body mass index (BMI) was 31 kg/m² (56% of patients had a BMI ≥30 kg/m²) and the mean age was 55 years (18% of patients ≥65 years of age).

In a pooled analysis of these four controlled clinical studies, the overall incidence of adverse reactions was 74% in patients treated with KAZANO compared to 75% treated with placebo. Overall discontinuation of therapy due to adverse reactions was 6.2% with KAZANO compared to 1.9% in placebo, 6.4% in metformin and 5.0% in alogliptin.

Adverse reactions reported in ≥4% of patients treated with KAZANO and more frequently than in patients who received alogliptin, metformin or placebo are summarized in Table 1.

Table 1. Adverse Reactions Reported in ≥4% of Patients Treated with KAZANO and More Frequently Than in Patients Receiving Either Alogliptin, Metformin or Placebo

	Number of Patients (%)			
	KAZANO*	Alogliptin†	Metformin‡	Placebo
	N=2794	N=222	N=1592	N=106
Upper respiratory tract infection	224 (8.0)	6 (2.7)	105 (6.6)	3 (2.8)
Nasopharyngitis	191 (6.8)	7 (3.2)	93 (5.8)	2 (1.9)
Diarrhea	155 (5.5)	4 (1.8)	105 (6.6)	3 (2.8)
Hypertension	154 (5.5)	5 (2.3)	96 (6.0)	6 (5.7)
Headache	149 (5.3)	11 (5.0)	74 (4.6)	3 (2.8)
Back pain	119 (4.3)	1 (0.5)	72 (4.5)	1 (0.9)
Urinary tract infection	116 (4.2)	4 (1.8)	59 (3.7)	2 (1.9)

*KAZANO – includes data pooled for patients receiving alogliptin 25 and 12.5 mg combined with various dose of metformin

†Alogliptin – includes data pooled for patients receiving alogliptin 25 and 12.5 mg

‡Metformin – includes data pooled for patients receiving various doses of metformin

Hypoglycemia

In a 26 week, double-blind, placebo-controlled study of alogliptin in combination with metformin, the number of patients reporting hypoglycemia was 1.9% in the alogliptin 12.5 mg with metformin HCl 500 mg, 5.3% in the alogliptin 12.5 mg with metformin HCl 1000 mg, 1.8% in the metformin HCl 500 mg and 6.3% in the metformin HCl 1000 mg treatment groups.

In a 26 week placebo-controlled study of alogliptin 25 mg administered once daily as add-on to metformin regimen, the number of patients reporting hypoglycemic events was 0% in the alogliptin with metformin and 2.9% in the placebo treatment groups.

In a 52 week, active-controlled, double-blind study of alogliptin once daily as add-on therapy to the combination of pioglitazone 30 mg and metformin compared to the titration of pioglitazone 30 mg to 45 mg and metformin, the number of patients reporting hypoglycemia was 4.5% in the alogliptin 25 mg with pioglitazone 30 mg and metformin group versus 1.5% in the pioglitazone 45 mg with metformin group.

In an interim analysis conducted in a 104-week, double-blind, active-controlled study of alogliptin 25 mg in combination with metformin, the number of patients reporting hypoglycemia was 1.4% in the alogliptin 25 mg with metformin group versus 23.8% in the glipizide with metformin group.

Alogliptin

A total of 14,778 patients with type 2 diabetes participated in 14 randomized, double-blind, controlled clinical trials of whom 9052 subjects were treated with alogliptin, 3469 subjects were treated with placebo and 2257 were treated with an active comparator. The mean duration of diabetes was seven years, the mean body mass index (BMI) was 31 kg/m² (49% of patients had a BMI \geq 30 kg/m²), and the mean age was 58 years (26% of patients \geq 65 years of age). The mean exposure to alogliptin was 49 weeks with 3348 subjects treated for more than one year.

In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse reactions was 73% in patients treated with alogliptin 25 mg compared to 75% with placebo and 70% with active comparator. Overall discontinuation of therapy due to adverse reactions was 6.8% with alogliptin 25 mg compared to 8.4% with placebo or 6.2% with active comparator.

Adverse reactions reported in ≥4% of patients treated with alogliptin 25 mg and more frequently than in patients who received placebo are summarized in Table 2.

Table 2. Adverse Reactions Reported in ≥4% Patients Treated with Alogliptin 25 mg and More Frequently Than in Patients Given Placebo in Pooled Studies

	Number of Patients (%)		
	Alogliptin 25 mg	Placebo	Active Comparator
	N=6447	N=3469	N=2257
Nasopharyngitis	309 (4.8)	152 (4.4)	113 (5.0)
Upper Respiratory Tract Infection	287 (4.5)	121 (3.5)	113 (5.0)
Headache	278 (4.3)	101 (2.9)	121 (5.4)

Hypoglycemia

Hypoglycemic events were documented based upon a blood glucose value and/or clinical signs and symptoms of hypoglycemia.

In the monotherapy study, the incidence of hypoglycemia was 1.5% in patients treated with alogliptin compared to 1.6% with placebo. The use of alogliptin as add-on therapy to glyburide or insulin did not increase the incidence of hypoglycemia compared to placebo. In a monotherapy study comparing alogliptin to a sulfonylurea in elderly patients, the incidence of hypoglycemia was 5.4% with alogliptin compared to 26% with glipizide.

In the EXAMINE trial, the incidence of investigator reported hypoglycemia was 6.7% in patients receiving alogliptin and 6.5% in patients receiving placebo. Serious adverse reactions of hypoglycemia were reported in 0.8% of patients treated with alogliptin and in 0.6% of patients treated with placebo.

Metformin Hydrochloride

Table 3. Most Common Adverse Reactions (≥5%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*

Adverse Reaction	Metformin Monotherapy (n=141)	Placebo (n=145)
	% of Patients	
Diarrhea	53.2	11.7
Nausea/vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1

Abdominal discomfort	6.4	4.8
Headache	5.7	4.8

*Reactions that were more common in metformin than placebo-treated patients

6.2 Laboratory Abnormalities

Alogliptin and Metformin Hydrochloride

No clinically meaningful differences were observed among treatment groups regarding hematology, serum chemistry or urinalysis results.

Metformin Hydrochloride

Metformin may lower serum vitamin B₁₂ concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on KAZANO, and any apparent abnormalities should be appropriately investigated and managed [see *Warnings and Precautions (5.6)*].

6.3 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Alogliptin

Acute pancreatitis, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and severe cutaneous adverse reactions, including Stevens-Johnson syndrome, hepatic enzyme elevations, fulminant hepatic failure, severe and disabling arthralgia and bullous pemphigoid, rhabdomyolysis, diarrhea, constipation, nausea, and ileus [see *Warnings and Precautions (5.2, 5.4, 5.5, 5.8, 5.9)*].

Metformin

Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

7 DRUG INTERACTIONS

Alogliptin

Alogliptin is primarily renally excreted. Cytochrome (CYP) P450-related metabolism is negligible. No significant drug-drug interactions were observed with the CYP-substrates or inhibitors tested or with renally excreted drugs [see *Clinical Pharmacology (12.3)*].

Metformin Hydrochloride

7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce nonanion gap, hyperchlloremic metabolic acidosis. Concomitant use of these drugs with KAZANO may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

7.2 Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see *Clinical Pharmacology (12.3)*]. Consider the benefits and risks of concomitant use.

7.3 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving KAZANO.

7.4 Insulin Secretagogues and Insulin

When used in an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.

7.5 The Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid. When such drugs are administered to a patient receiving KAZANO, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving KAZANO, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with KAZANO or alogliptin in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see Data]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see Clinical Considerations].

Concomitant administration of alogliptin and metformin in pregnant rats during the period of organogenesis did not cause adverse developmental effects in offspring at maternal exposures up to 28 times and two times the 25 mg and 2000 mg clinical doses, respectively [see Data].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c > 7 and has been reported to be as high as 20-25% in women with HbA1c > 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major malformations, still birth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies do not report a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Alogliptin and Metformin

Concomitant administration of alogliptin and metformin in pregnant rats during the period of organogenesis did not cause adverse developmental effects in offspring at a dose of 100 mg/kg alogliptin and 150 mg/kg metformin , or approximately 28 and two times the clinical dose of alogliptin (25 mg) and metformin (2000 mg), respectively based on plasma drug exposure (AUC).

Alogliptin

Alogliptin administered to pregnant rabbits and rats during the period of organogenesis did not cause adverse developmental effects at doses of up to 200 mg/kg and 500 mg/kg, or 149 times and 180 times the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC). Placental transfer of alogliptin into the fetus was observed following oral dosing to pregnant rats.

No adverse developmental outcomes were observed in offspring when alogliptin was administered to pregnant rats during gestation and lactation at doses up to 250 mg/kg (approximately 95 times the 25 mg clinical dose, based on AUC).

Metformin Hydrochloride

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about two to six times a clinical dose of 2000 mg based on body surface area (mg/m²) for rats and rabbits, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KAZANO or alogliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Alogliptin is present in rat milk. Limited published studies report that metformin is present in human milk [see *Data*]. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KAZANO and any potential adverse effects on the breastfed infant from KAZANO or from the underlying maternal condition.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio (based on AUC) ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

There is the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some premenopausal anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of KAZANO in pediatric patients have not been established.

8.5 Geriatric Use

Alogliptin and Metformin Hydrochloride

Elderly patients are more likely to have decreased renal function. Monitor renal function in the elderly more frequently [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

Of the total number of patients (N = 2095) in clinical safety and efficacy studies, 343 (16.4%) patients were 65 years and older and 37 (1.8%) patients were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this and other reported clinical experiences have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be excluded.

Alogliptin

Of the total number of patients (N=9052) in clinical safety and efficacy studies treated with alogliptin, 2257 (24.9%) patients were 65 years and older and 386 (4.3%) patients were 75 years and older. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients.

Metformin Hydrochloride

Controlled studies of metformin did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal and cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [see *Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. KAZANO is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m² [see *Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. KAZANO is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.1)*].

10 OVERDOSAGE

Alogliptin

The highest doses of alogliptin administered in clinical trials were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes (equivalent to 32 times and 16 times the maximum recommended clinical dose of 25 mg, respectively). No serious adverse reactions were observed at these doses.

In the event of an overdose, it is reasonable to institute the necessary clinical monitoring and supportive therapy as dictated by the patient's clinical status. Per clinical judgment, it may be reasonable to initiate removal of unabsorbed material from the gastrointestinal tract.

Alogliptin is minimally dialyzable; over a three-hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to be beneficial in an overdose situation. It is not known if alogliptin is dialyzable by peritoneal dialysis.

Metformin Hydrochloride

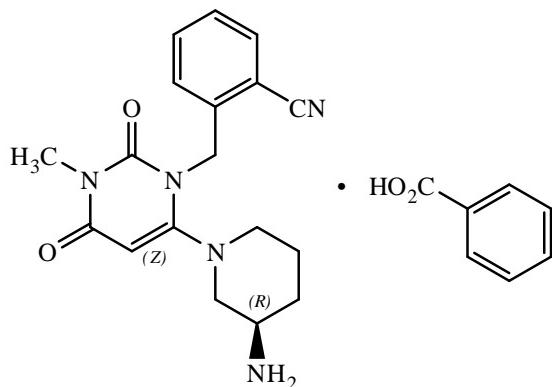
Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions (5.1)*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

11 DESCRIPTION

KAZANO tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: alogliptin and metformin hydrochloride.

Alogliptin

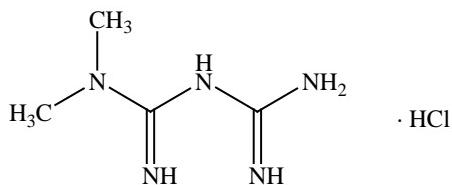
Alogliptin is a selective, orally bioavailable inhibitor of the enzymatic activity of dipeptidyl peptidase-4 (DPP-4). Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({(3*R*)-3-aminopiperidin-1-yl}-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)benzonitrile monobenzoate. It has a molecular formula of $C_{18}H_{21}N_5O_2 \bullet C_7H_6O_2$ and a molecular weight of 461.51 daltons; the structural formula is:



Alogliptin benzoate is a white to off-white crystalline powder containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol and very slightly soluble in octanol and isopropyl acetate.

Metformin Hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \bullet HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



KAZANO is available as a tablet for oral administration containing 17 mg alogliptin benzoate equivalent to 12.5 mg alogliptin and:

- 500 mg metformin hydrochloride (12.5 mg/500 mg) or
- 1000 mg metformin hydrochloride (12.5 mg/1000 mg).

KAZANO tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, povidone, crospovidone, and magnesium stearate; the tablets are film-coated with hypromellose 2910, talc, titanium dioxide and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alogliptin and Metformin Hydrochloride

KAZANO combines two antihyperglycemic agents with complementary and distinct mechanisms of action to improve glycemic control in patients with type 2 diabetes: alogliptin, a selective inhibitor of DPP-4, and metformin HCl, a member of the biguanide class.

Alogliptin

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Metformin Hydrochloride

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in special circumstances [see *Warnings and Precautions* (5.7)] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Alogliptin

Single-dose administration of alogliptin to healthy subjects resulted in a peak inhibition of DPP-4 within two to three hours after dosing. The peak inhibition of DPP-4 exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24 hours to active GLP-1 were three- to four-fold greater with alogliptin (at doses of 25 to 200 mg) than placebo. In a 16 week, double-blind, placebo-controlled study, alogliptin 25 mg demonstrated decreases in postprandial glucagon while increasing postprandial active GLP-1 levels compared to placebo over an eight hour period following a standardized meal. It is unclear how these findings relate to changes in overall glycemic control in patients with type 2 diabetes mellitus. In this study, alogliptin 25 mg demonstrated decreases in two-hour postprandial glucose compared to placebo (-30 mg/dL versus 17 mg/dL, respectively).

Multiple-dose administration of alogliptin to patients with type 2 diabetes also resulted in a peak inhibition of DPP-4 within one to two hours and exceeded 93% across all doses (25 mg, 100 mg and 400 mg) after a single dose and after 14 days of once-daily dosing. At these doses of alogliptin, inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing.

12.3 Pharmacokinetics

Absorption and Bioavailability

Alogliptin and Metformin Hydrochloride

In bioequivalence studies of KAZANO, the area under the plasma concentration curve (AUC) and maximum concentration (C_{max}) of both the alogliptin and the metformin component following a single dose of the combination tablet were bioequivalent to the alogliptin 12.5 mg concomitantly administered with metformin HCl 500 or 1000 mg tablets under fasted conditions in healthy subjects. Administration of KAZANO with food resulted in no change in total exposure (AUC) of alogliptin and metformin. Mean peak plasma concentrations of alogliptin and metformin were decreased by 13% and 28%, respectively, when administered with food. There was no change in time to peak plasma concentrations (T_{max}) for alogliptin under fed conditions, however, there was a delayed T_{max} for metformin of 1.5 hours. These changes are not likely to be clinically significant.

Alogliptin

The absolute bioavailability of alogliptin is approximately 100%. Administration of alogliptin with a high-fat meal results in no significant change in total and peak exposure to alogliptin. Alogliptin may therefore be administered with or without food.

Metformin Hydrochloride

The absolute bioavailability of metformin following administration of a 500 mg metformin HCl tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1500 mg and 850 mg to 2550 mg indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin HCl with food compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Alogliptin

Following a single, 12.5 mg intravenous infusion of alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L, indicating that the drug is well distributed into tissues.

Alogliptin is 20% bound to plasma proteins.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate release metformin HCl tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally less than 1 mcg/mL. During controlled clinical trials, which served as the basis for approval for metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Alogliptin

Alogliptin does not undergo extensive metabolism and 60% to 71% of the dose is excreted as unchanged drug in the urine.

Two minor metabolites were detected following administration of an oral dose of [¹⁴C] alogliptin, *N*-demethylated, M-I (less than 1% of the parent compound), and *N*-acetylated alogliptin, M-II (less than 6% of the parent compound). M-I is an active metabolite and is an inhibitor of DPP-4 similar to the parent molecule; M-II does not display any inhibitory activity toward DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

Alogliptin exists predominantly as the (*R*)-enantiomer (more than 99%) and undergoes little or no chiral conversion *in vivo* to the (*S*)-enantiomer. The (*S*)-enantiomer is not detectable at the 25 mg dose.

Metformin Hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Excretion and Elimination

Alogliptin

The primary route of elimination of [¹⁴C] alogliptin-derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr.

Metformin Hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Renal Impairment

Metformin Hydrochloride

In patients with decreased renal function (based on measured creatine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [see *Contraindications* (4), *Warnings and Precautions* (5.1)].

Hepatic Impairment

Alogliptin

Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment (Child-Pugh Grade B) compared to healthy subjects. The magnitude of these reductions is not considered to be clinically meaningful. Patients with severe hepatic impairment (Child-Pugh Grade C) have not been studied.

Metformin Hydrochloride

No pharmacokinetic studies of metformin have been conducted in subjects with hepatic impairment.

Gender**Alogliptin**

No dose adjustment is necessary based on gender. Gender did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Metformin Hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride tablets was comparable in males and females.

Geriatric

Due to declining renal function in the elderly, measurement of creatinine clearance should be obtained prior to initiation of therapy.

Alogliptin

No dose adjustment is necessary based on age. Age did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Metformin Hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatrics

Studies characterizing the pharmacokinetics of alogliptin in pediatric patients have not been performed.

Race**Alogliptin**

No dose adjustment of alogliptin is necessary based on race. Race (white, black and Asian) did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Metformin Hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51) and Hispanics (n=24).

Drug Interactions**Alogliptin and Metformin Hydrochloride**

Administration of alogliptin 100 mg once daily with metformin HCl 1000 mg twice daily for six days had no meaningful effect on the pharmacokinetics of alogliptin or metformin.

Specific pharmacokinetic drug interaction studies with KAZANO have not been performed, although such studies have been conducted with the individual components of KAZANO (alogliptin and metformin).

Alogliptin**In Vitro Assessment of Drug Interactions**

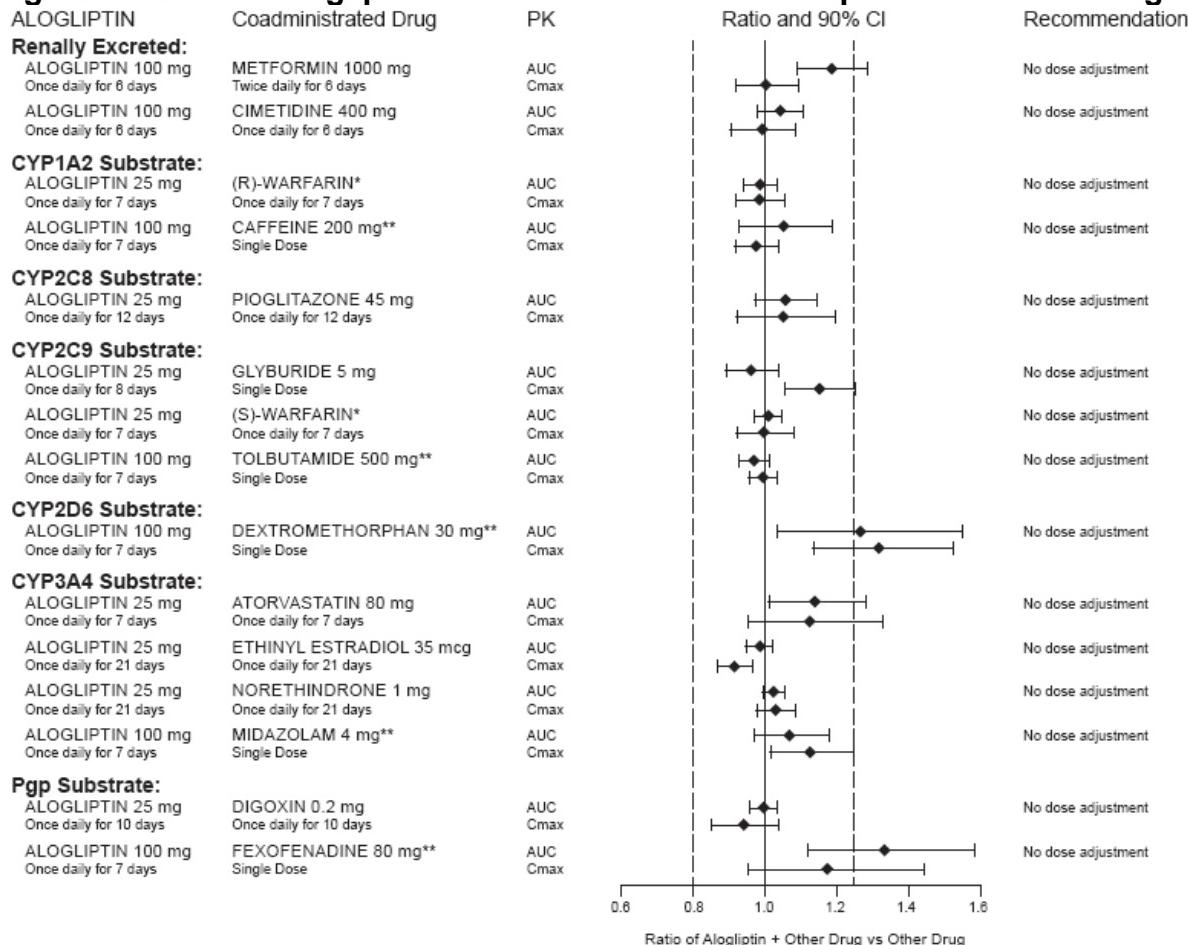
In vitro studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

Effects of Alogliptin on the Pharmacokinetics of Other Drugs

In clinical studies, alogliptin did not meaningfully increase the systemic exposure to the following drugs that are metabolized by CYP isozymes or excreted unchanged in urine (*Figure 1*). No dose adjustment of alogliptin is recommended based on results of the described pharmacokinetic studies.

Figure 1. Effect of Alogliptin on the Pharmacokinetic Exposure to Other Drugs

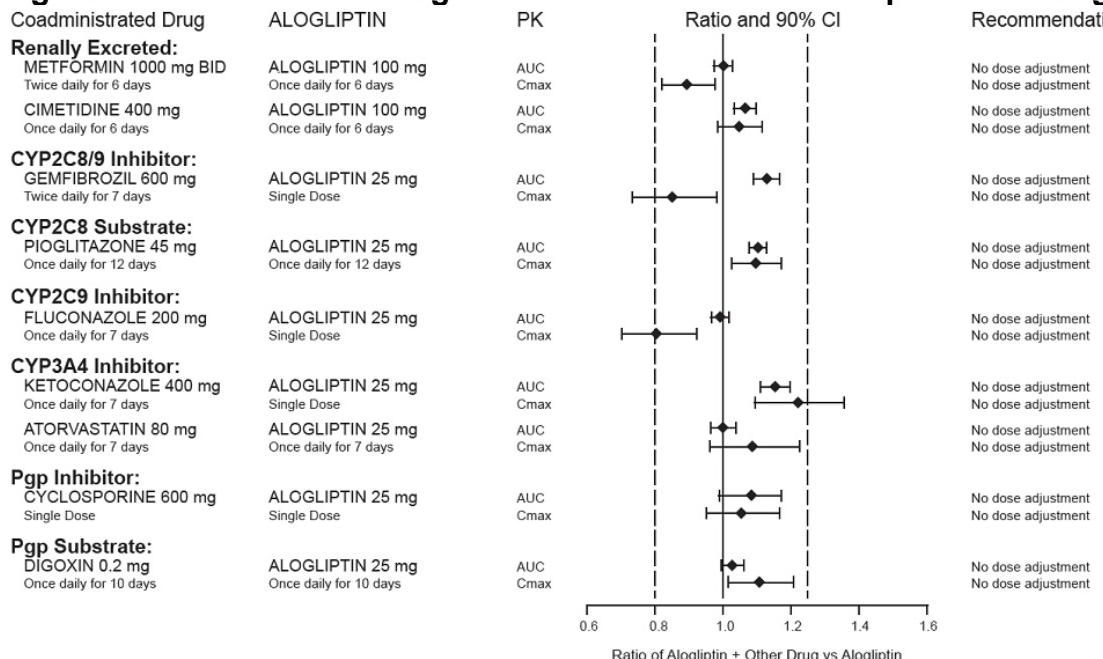


*Warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).

**Caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4 substrate) and fexofenadine (P-gp substrate) were administered as a cocktail.

Effects of Other Drugs on the Pharmacokinetics of Alogliptin

There are no clinically meaningful changes in the pharmacokinetics of alogliptin when alogliptin is administered concomitantly with the drugs described below (*Figure 2*).

Figure 2. Effect of Other Drugs on the Pharmacokinetic Exposure of Alogliptin**Metformin Hydrochloride**

Pharmacokinetic drug interaction studies have been performed on metformin (Tables 4 and 5).

Table 4. Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00	
			AUC [†]	C _{max}
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg [‡]	0.98 [§]	0.99 [§]
Furosemide	40 mg	850 mg	1.09 [§]	1.22 [§]
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05 [§]	1.07 [§]
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin [see Warnings and Precautions (5) and Drug Interactions (7)].				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis [see Warnings and Precautions (5) and Drug Interactions (7)]				
Topiramate	100 mg [¶]	500 mg [¶]	1.25 [¶]	1.17

*All metformin and coadministered drugs were given as single doses

†AUC = AUC_{0-∞}

‡metformin hydrochloride extended-release tablets 500 mg

§Ratio of arithmetic means

¶At steady-state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC_{0-12h}

Table 5. Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00	
			AUC [†]	C _{max}
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg [‡]	0.78 [§]	0.63 [§]
Furosemide	40 mg	850 mg	0.87 [§]	0.69 [§]
Nifedipine	10 mg	850 mg	1.10 [‡]	1.08
Propranolol	40 mg	850 mg	1.01 [‡]	0.94
Ibuprofen	400 mg	850 mg	0.97 [¶]	1.01 [¶]
Cimetidine	400 mg	850 mg	0.95 [‡]	1.01

*All metformin and coadministered drugs were given as single doses

[†]AUC = AUC_{0-∞}

[‡]AUC₀₋₂₄ hr reported

[§]Ratio of arithmetic means, p-value of difference <0.05

[¶]Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Alogliptin and Metformin Hydrochloride

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with KAZANO. The following data are based on findings in studies performed with alogliptin or metformin individually.

Alogliptin

Rats were administered oral doses of 75, 400 and 800 mg/kg alogliptin for two years. No drug-related tumors were observed up to 75 mg/kg or approximately 32 times the maximum recommended clinical dose of 25 mg, based on area under the plasma concentration curve (AUC) exposure. At higher doses (approximately 308 times the maximum recommended clinical dose of 25 mg), a combination of thyroid C-cell adenomas and carcinomas increased in male but not female rats. No drug-related tumors were observed in mice after administration of 50, 150 or 300 mg/kg alogliptin for two years, or up to approximately 51 times the maximum recommended clinical dose of 25 mg, based on AUC exposure.

Alogliptin was not mutagenic or clastogenic, with and without metabolic activation, in the Ames test with *S. typhimurium* and *E. coli* or the cytogenetic assay in mouse lymphoma cells. Alogliptin was negative in the *in vivo* mouse micronucleus study.

In a fertility study in rats, alogliptin had no adverse effects on early embryonic development, mating or fertility, at doses up to 500 mg/kg, or approximately 172 times the clinical dose based on plasma drug exposure (AUC).

Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg and 1500 mg/kg, respectively. These doses are both approximately four times the maximum recommended human

daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells) or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

14 CLINICAL STUDIES

The coadministration of alogliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on either diet and exercise alone, on metformin alone or metformin in combination with a thiazolidinedione.

There have been no clinical efficacy studies conducted with KAZANO; however, bioequivalence of KAZANO with coadministered alogliptin and metformin tablets was demonstrated, and efficacy of the combination of alogliptin and metformin has been demonstrated in three Phase 3 efficacy studies.

A total of 2095 patients with type 2 diabetes were randomized in three double-blind, placebo- or active-controlled clinical safety and efficacy studies conducted to evaluate the effects of KAZANO on glycemic control. The racial distribution of patients exposed to study medication was 69.2% white, 16.3% Asian, 6.5% black and 8.0% other racial groups. The ethnic distribution was 24.3% Hispanic. Patients had an overall mean age of approximately 54.4 years (range 22 to 80 years). In patients with type 2 diabetes, treatment with KAZANO produced clinically meaningful and statistically significant improvements in A1C versus comparator. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in hemoglobin A1c (A1C) with KAZANO appears to be related to the degree of A1C elevation at baseline.

Alogliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

In a 26 week, double-blind, placebo-controlled study, a total of 784 patients inadequately controlled on diet and exercise alone (mean baseline A1C = 8.4%) were randomized to one of seven treatment groups: placebo; metformin HCl 500 mg or metformin HCl 1000 mg twice daily, alogliptin 12.5 mg twice daily, or alogliptin 25 mg daily; alogliptin 12.5 mg in combination with metformin HCl 500 mg or metformin HCl 1000 mg twice daily. Both coadministration treatment arms (alogliptin 12.5 mg + metformin HCl 500 mg and alogliptin 12.5 mg + metformin HCl 1000 mg) resulted in significant improvements in A1C (*Figure 3*) and FPG when compared with their respective individual alogliptin and metformin component regimens (*Table 6*). Coadministration treatment arms demonstrated improvements in two-hour postprandial glucose (PPG) compared to alogliptin alone or metformin alone (*Table 6*). A total of 12% of patients receiving alogliptin 12.5 mg + metformin HCl 500 mg, 3% of patients receiving alogliptin 12.5 mg + metformin HCl 1000 mg, 17% of patients receiving alogliptin 12.5 mg, 23% of patients receiving metformin HCl 500 mg, 11% of patients receiving metformin HCl 1000 mg and 39% of patients receiving placebo required glycemic rescue.

Improvements in A1C were not affected by gender, age, race or baseline BMI. The mean decrease in body weight was similar between metformin alone and alogliptin when coadministered with metformin. Lipid effects were neutral.

Table 6. Glycemic Parameters at Week 26 for Alogliptin and Metformin Alone and in Combination in Patients with Type 2 Diabetes

	Placebo	Alogliptin 12.5 mg twice daily	Metformin HCl 500 mg twice daily	Metformin HCl 1000 mg twice daily	Alogliptin 12.5 mg + Metformin HCl 500 mg twice daily	Alogliptin 12.5 mg + Metformin HCl 1000 mg twice daily
A1C (%)*	N=102	N=104	N=103	N=108	N=102	N=111
Baseline (mean)	8.5	8.4	8.5	8.4	8.5	8.4
Change from baseline (adjusted mean [†])	0.1	-0.6	-0.7	-1.1	-1.2	-1.6
Difference from metformin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-0.6 [‡] (-0.9, -0.3)	-0.4 [‡] (-0.7, -0.2)
Difference from alogliptin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-0.7 [‡] (-1.0, -0.4)	-1.0 [‡] (-1.3, -0.7)
% of Patients (n/N) achieving A1C <7% [§]	4% (4/102)	20% (21/104)	27% (28/103)	34% (37/108)	47% [‡] (48/102)	59% [‡] (66/111)
FPG (mg/dL)*	N=105	N=106	N=106	N=110	N=106	N=112
Baseline (mean)	187	177	180	181	176	185
Change from baseline (adjusted mean [†])	12	-10	-12	-32	-32	-46
Difference from metformin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-20 [‡] (-33, -8)	-14 [‡] (-26, -2)
Difference from alogliptin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-22 [‡] (-35, -10)	-36 [‡] (-49, -24)
2-Hour PPG (mg/dL)[¶]	N=26	N=34	N=28	N=37	N=31	N=37
Baseline (mean)	263	272	247	266	261	268
Change from baseline (adjusted mean [†])	-21	-43	-49	-54	-68	-86 [‡]
Difference from metformin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-19 (-49, 11)	-32 [‡] (-58, -5)
Difference from alogliptin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-25 (-53, 3)	-43 [‡] (-70, -16)

*Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue

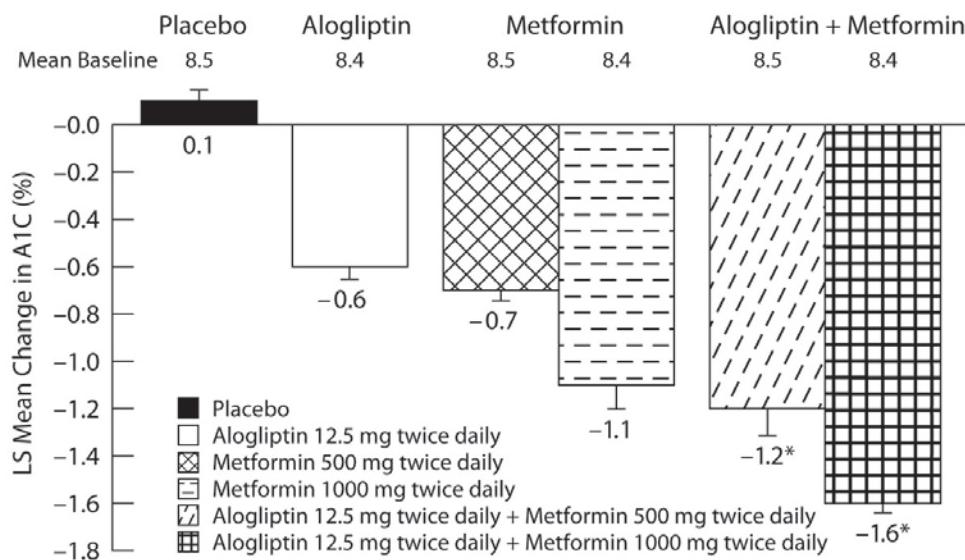
[†]Least squares means adjusted for treatment, geographic region and baseline value

[‡]p<0.05 when compared to metformin and alogliptin alone

[§]Compared using logistic regression

[¶]Intent-to-treat population using data available at Week 26

Figure 3. Change from Baseline A1C at Week 26 with Alogliptin and Metformin Alone and Alogliptin in Combination with Metformin



Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue.

*P<0.001 when compared to metformin and alogliptin alone.

Alogliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

In a 26 week, double-blind, placebo-controlled study, a total of 527 patients already on metformin (mean baseline A1C = 8%) were randomized to receive alogliptin 12.5 mg, alogliptin 25 mg, or placebo once daily. Patients were maintained on a stable dose of metformin HCl (median daily dose = 1700 mg) during the treatment period. Alogliptin 25 mg in combination with metformin resulted in statistically significant improvements from baseline in A1C and FPG at Week 26, when compared to placebo (*Table 7*). A total of 8% of patients receiving alogliptin 25 mg and 24% of patients receiving placebo required glycemic rescue. Improvements in A1C were not affected by gender, age, race, baseline BMI or baseline metformin dose.

The mean decrease in body weight was similar between alogliptin 25 mg and placebo when given in combination with metformin. Lipid effects were also neutral.

Table 7. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of Alogliptin as Add-on Therapy to Metformin*

	Alogliptin 25 mg + Metformin	Placebo + Metformin
A1C (%)	N=203	N=103
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean [†])	-0.6	-0.1
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-0.5 [‡] (-0.7, -0.3)	-
% of patients (n/N) achieving A1C ≤7% [‡]	44% (92/207) [‡]	18% (19/104)
FPG (mg/dL)	N=204	N=104
Baseline (mean)	172	180
Change from baseline (adjusted mean [†])	-17	0
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-17 [‡] (-26, -9)	-

*Intent-to-treat population using last observation on study.

[†]Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose.

[‡]p<0.001 compared to placebo.

Alogliptin Add-On Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Pioglitazone

In a 52 week, active-comparator study, a total of 803 patients inadequately controlled (mean baseline A1C = 8.2%) on a current regimen of pioglitazone 30 mg and metformin were randomized to either receive the addition of once-daily alogliptin 25 mg or the titration of pioglitazone 30 mg to 45 mg following a four-week single-blind, placebo run-in period. Patients were maintained on a stable dose of metformin HCl (median daily dose = 1700 mg). Patients who failed to meet prespecified hyperglycemic goals during the 52 week treatment period received glycemic rescue therapy.

In combination with pioglitazone and metformin, alogliptin 25 mg was shown to be statistically superior in lowering A1C and FPG compared with the titration of pioglitazone from 30 to 45 mg at Week 26 and at Week 52 (*Table 8*). A total of 11% of patients in the alogliptin 25 mg in combination with pioglitazone 30 mg and metformin treatment group and 22% of patients in the up titration of pioglitazone in combination with metformin treatment group required glycemic rescue. Improvements in A1C were not affected by gender, age, race or baseline BMI.

The mean increase in body weight was similar in both treatment arms. Lipid effects were neutral.

Table 8. Glycemic Parameters at Week 52 in an Active-Controlled Study of Alogliptin as Add-On Combination Therapy to Metformin and Pioglitazone*

	Alogliptin 25 mg + Pioglitazone 30 mg + Metformin	Pioglitazone 45 mg + Metformin
A1C (%)	N=397	N=394
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean [†])	-0.7	-0.3
Difference from pioglitazone 45 mg + metformin* (adjusted mean [†] with 95% confidence interval)	-0.4 [‡] (-0.5, -0.3)	-
% of Patients (n/N) achieving A1C ≤7%	33% (134/404) [§]	21% (85/399)
Fasting Plasma Glucose (mg/dL)[‡]	N=399	N=396
Baseline (mean)	162	162
Change from baseline (adjusted mean [†])	-15	-4
Difference from pioglitazone 45 mg + metformin (adjusted mean [†] with 95% confidence interval)	-11 [§] (-16, -6)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose[‡]Noninferior and statistically superior to metformin + pioglitazone at the 0.025 one-sided significance level[§]p<0.001 compared to pioglitazone 45 mg + metformin

Cardiovascular Safety Trial

A randomized, double-blind, placebo-controlled cardiovascular outcomes trial (EXAMINE) was conducted to evaluate the cardiovascular risk of alogliptin. The trial compared the risk of major adverse cardiovascular events (MACE) between alogliptin (N=2701) and placebo (N=2679) when added to standard of care therapies for diabetes and atherosclerotic vascular disease (ASCVD). The trial was event driven and patients were followed until a sufficient number of primary outcome events accrued.

Eligible patients were adults with type 2 diabetes who had inadequate glycemic control at baseline (e.g., HbA1c >6.5%) and had been hospitalized for an acute coronary syndrome event (e.g., acute myocardial infarction or unstable angina requiring hospitalization) 15 to 90 days prior to randomization. The dose of alogliptin was based on estimated renal function at baseline per dosage and administration recommendations. The average time between an acute coronary syndrome event and randomization was approximately 48 days.

The mean age of the population was 61 years. Most patients were male (68%), Caucasian (73%), and were recruited from outside of the United States (86%). Asian and Black patients contributed 20% and 4% of the total population, respectively. At the time of randomization patients had a

diagnosis of type 2 diabetes mellitus for approximately 9 years, 87% had a prior myocardial infarction and 14% were current smokers. Hypertension (83%) and renal impairment (27% with an eGFR ≤ 60 ml/min/1.73 m 2) were prevalent co-morbid conditions. Use of medications to treat diabetes (e.g., metformin 73%, sulfonylurea 54%, insulin 41%), and ASCVD (e.g., statin 94%, aspirin 93%, renin-angiotensin system blocker 88%, beta-blocker 87%) was similar between patients randomized to alogliptin and placebo at baseline. During the trial, medications to treat diabetes and ASCVD could be adjusted to ensure care for these conditions adhered to standard of care recommendations set by local practice guidelines.

The primary endpoint in EXAMINE was the time to first occurrence of a MACE defined as the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. The study was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE. The median exposure to study drug was 526 days and 95% of the patients were followed to study completion or death.

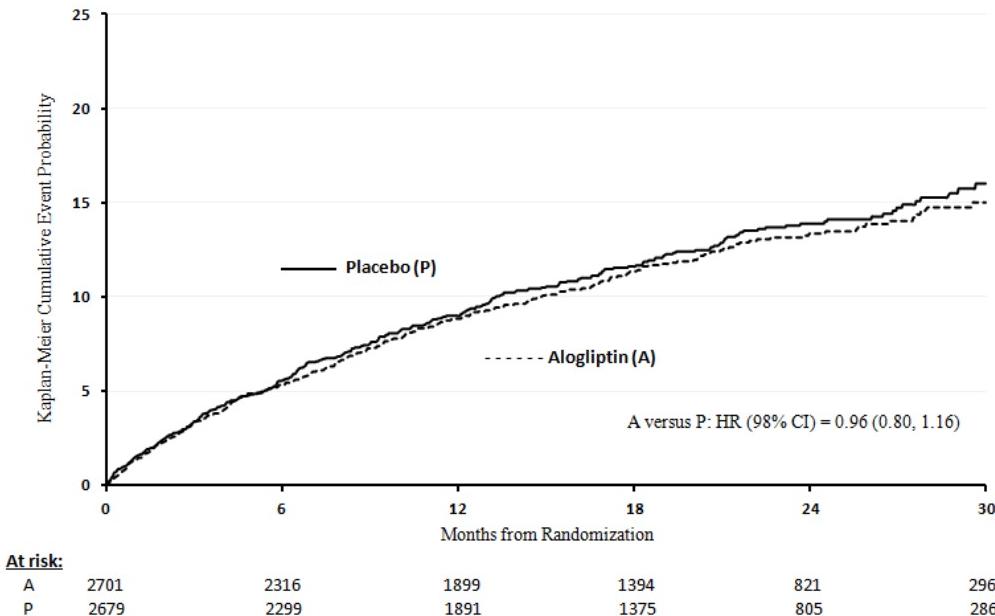
Table 9 shows the study results for the primary MACE composite endpoint and the contribution of each component to the primary MACE endpoint. The upper bound of the confidence interval was 1.16 and excluded a risk margin larger than 1.3.

Table 9. Patients with MACE in EXAMINE

	Alogliptin		Placebo		Hazard Ratio
	Number of Patients (%)	Rate per 100 PY*	Number of Patients (%)	Rate per 100 PY*	(98% CI)
	N=2701		N=2679		
Composite of first event of CV death, nonfatal MI or nonfatal stroke (MACE)	305 (11.3)	7.6	316 (11.8)	7.9	0.96 (0.80, 1.16)
CV Death	89 (3.3)	2.2	111 (4.1)	2.8	
Non-fatal MI	187 (6.9)	4.6	173 (6.5)	4.3	
Non-fatal stroke	29 (1.1)	0.7	32 (1.2)	0.8	

*Patient Years (PY)

The Kaplan-Meier based cumulative event probability is presented in Figure 4 for the time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for placebo and alogliptin overlap throughout the duration of the study. The observed incidence of MACE was highest within the first 60 days after randomization in both treatment arms (14.8 MACE per 100 PY), decreased from day 60 to the end of the first year (8.4 per 100 PY) and was lowest after 1 year of follow-up (5.2 per 100 PY).

Figure 4. Observed Cumulative Rate of MACE in EXAMINE

The rate of all cause death was similar between treatment arms with 153 (3.6 per 100 PY) recorded among patients randomized to alogliptin and 173 (4.1 per 100 PY) among patients randomized to placebo. A total of 112 deaths (2.9 per 100 PY) among patients on alogliptin and 130 among patients on placebo (3.5 per 100 PY) were adjudicated as cardiovascular deaths.

16 HOW SUPPLIED/STORAGE AND HANDLING

KAZANO tablets are available in the following strengths and packages:

12.5 mg/500 mg tablet: pale yellow, oblong, film-coated tablets with "12.5/500" debossed on one side and "322M" debossed on the other side, available in:

NDC 64764-335-60 Bottles of 60 tablets

NDC 64764-335-80 Bottles of 180 tablets

NDC 64764-335-77 Bottles of 500 tablets

12.5 mg/1000 mg tablet: pale yellow, oblong, film-coated tablets with "12.5/1000" debossed on one side and "322M" debossed on the other side, available in:

NDC 64764-337-60 Bottles of 60 tablets

NDC 64764-337-80 Bottles of 180 tablets

NDC 64764-337-77 Bottles of 500 tablets

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

- Inform patients of the potential risks and benefits of KAZANO.

- The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in *Warnings and Precautions* (5.1), should be explained to patients. Patients should be advised to discontinue KAZANO immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of KAZANO, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
- Patients should be informed that acute pancreatitis has been reported during use of alogliptin. Patients should be informed that persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue KAZANO and contact their physician if persistent severe abdominal pain occurs.
- Patients should be informed of the signs and symptoms of heart failure. Before initiating KAZANO, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Patients should be instructed to contact their healthcare providers as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight, or swelling of the feet.
- Patients should be informed that allergic reactions have been reported during use of alogliptin and metformin. If symptoms of allergic reactions (including skin rash, hives and swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing) occur, patients should be instructed to discontinue KAZANO and seek medical advice promptly.
- Patients should be informed that postmarketing reports of liver injury, sometimes fatal, have been reported during use of alogliptin. If signs or symptoms of liver injury occur, patients should be instructed to discontinue KAZANO and seek medical advice promptly.
- Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with KAZANO.
- Instruct patients to inform their doctor that they are taking KAZANO prior to any surgical or radiological procedure, as temporary discontinuation of KAZANO may be required until renal function has been confirmed to be normal [see *Warnings and Precautions* (5.1)].
- Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving KAZANO.
- Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue or insulin is used in combination with KAZANO. Explain the risks, symptoms and appropriate management of hypoglycemia.
- Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.
- Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [see *Warnings and Precautions* (5.10)].
- Instruct patients to take KAZANO only as prescribed twice daily. KAZANO should be taken with food. If a dose is missed, advise patients not to double their next dose.
- Patients should be informed that the tablets must never be split.

- Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effects on ovulation [see *Use in Specific Populations (8.3)*].

Instruct patients to read the Medication Guide before starting KAZANO therapy and to reread each time the prescription is refilled. Instruct patients to inform their healthcare provider if an unusual symptom develops or if a symptom persists or worsens.

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MEDICATION GUIDE

KAZANO (Kah-ZAHN-oh) (alogliptin and metformin HCl) tablets

Read this Medication Guide carefully before you start taking KAZANO and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about KAZANO, ask your doctor or pharmacist.

What is the most important information I should know about KAZANO?

KAZANO can cause serious side effects, including:

1. **Lactic Acidosis.** Metformin, one of the medicines in KAZANO, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with KAZANO if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems listed above. Your doctor may decide to stop KAZANO for a while if you have any of these things.

KAZANO can have other serious side effects. See “What are the possible side effects of KAZANO?”

2. **Inflammation of the pancreas (pancreatitis).** Alogliptin, one of the medicines in KAZANO, may cause pancreatitis, which may be severe. Certain medical conditions make you more likely to get pancreatitis.

Before you start taking KAZANO:

Tell your doctor if you have ever had:

- pancreatitis
- kidney problems
- liver problems

Stop taking KAZANO and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

3. **Heart failure:**

Before you start taking KAZANO:

Tell your healthcare provider if you have ever had heart failure or have problems with your kidneys.

Contact your healthcare provider right away if you have any of the following symptoms:

- increasing shortness of breath or
- an unusually fast increase in
- swelling of feet, ankles, or legs

trouble breathing especially when lying down weight

These may be symptoms of heart failure.

What is KAZANO?

- KAZANO contains 2 prescription diabetes medicines, alogliptin (NESINA) and metformin hydrochloride.
- KAZANO is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- KAZANO is not for people with type 1 diabetes.
- KAZANO is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if KAZANO is safe and effective in children under the age of 18.

Who should not take KAZANO?

Do not take KAZANO if you:

- have severe kidney problems
- have a condition called metabolic acidosis or have had diabetic ketoacidosis (increased ketones in your blood or urine)
- are going to get an injection of dye or contrast agents for an x-ray procedure, KAZANO may need to be stopped for a short time. Talk to your doctor about when you should stop KAZANO and when you should start KAZANO again
- are allergic to alogliptin (NESINA) or metformin or any of the ingredients in KAZANO or have had a serious allergic (hypersensitivity) reaction to alogliptin or metformin. See the end of this Medication Guide for a complete list of the ingredients in KAZANO

Symptoms of a serious allergic reaction to KAZANO may include:

- swelling of your face, lips, throat and other areas on your skin
- difficulty with swallowing or breathing
- raised, red areas on your skin (hives)
- skin rash, itching, flaking or peeling

If you have any of these symptoms, stop taking KAZANO and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before and during treatment with KAZANO?

Before you take KAZANO, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis)
- have severe kidney or liver problems
- have heart problems, including congestive heart failure
- are going to get an injection of dye or contrast agents for an x-ray procedure, KAZANO may need to be stopped for a short time. Talk to your doctor about when you should stop KAZANO and when you should start KAZANO again
- drink alcohol very often or drink a lot of alcohol in short-term “binge” drinking
- have other medical conditions
- are pregnant or plan to become pregnant. It is not known if KAZANO will harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant
- are breastfeeding or plan to breastfeed. It is not known whether KAZANO passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking KAZANO

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist before you start any new medicine.

KAZANO may affect the way other medicines work, and other medicines may affect how KAZANO works. Contact your doctor before you start or stop other types of medicines.

How should I take KAZANO?

- Take KAZANO exactly as your doctor tells you to take it.
- Take KAZANO 2 times each day.
- Take KAZANO with food to lower your chances of having an upset stomach.
- Do not break or cut KAZANO tablets before swallowing.
- Your doctor may need to change your dose of KAZANO to control your blood glucose. Do not change your dose unless told to do so by your doctor.

- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose, and take the next dose at your regular time. Do not take 2 doses of KAZANO at the same time.
- If you take too much KAZANO, call your doctor or go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start KAZANO and during treatment as needed. Your doctor may ask you to stop taking KAZANO based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of KAZANO?

KAZANO can cause serious side effects, including:

- See “**What is the most important information I should know about KAZANO?**”
- **Allergic (hypersensitivity) reactions**, such as:

<input type="radio"/> swelling of your face, lips, throat and other areas on your skin <input type="radio"/> raised, red areas on your skin (hives)	<input type="radio"/> difficulty swallowing or breathing <input type="radio"/> skin rash, itching, flaking or peeling
--	--

 If you have these symptoms, stop taking KAZANO and contact your doctor right away.
- **Liver problems.** Call your doctor right away if you have unexplained symptoms, such as:

<input type="radio"/> nausea or vomiting <input type="radio"/> loss of appetite	<input type="radio"/> stomach pain <input type="radio"/> dark urine	<input type="radio"/> unusual or unexplained tiredness <input type="radio"/> yellowing of your skin or the whites of your eyes
--	--	---
- **Low blood sugar (hypoglycemia).** If you take KAZANO with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take KAZANO. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, and then call your doctor. Signs and symptoms of low blood sugar may include:

<input type="radio"/> shaking or feeling jittery <input type="radio"/> sweating	<input type="radio"/> fast heartbeat <input type="radio"/> change in vision	<input type="radio"/> hunger <input type="radio"/> headache	<input type="radio"/> change in mood <input type="radio"/> confusion	<input type="radio"/> dizziness
--	--	--	---	---------------------------------
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in KAZANO, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in KAZANO, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking KAZANO.

The most common side effects of KAZANO include:

- | | | |
|---|--|---|
| <input type="radio"/> cold-like symptoms (upper respiratory tract infection)
<input type="radio"/> increase in blood pressure
<input type="radio"/> urinary tract infection | <input type="radio"/> stuffy or runny nose and sore throat
<input type="radio"/> headache | <input type="radio"/> diarrhea
<input type="radio"/> back pain |
|---|--|---|

Taking KAZANO with food can help lessen the common stomach side effects of metformin that usually happen at the beginning of treatment. If you have unexplained stomach problems, tell your doctor. Stomach problems that start later, during treatment, may be a sign of something more serious.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KAZANO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KAZANO?

- Store KAZANO at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container of KAZANO tightly closed.

Keep KAZANO and all medicines out of the reach of children.

General information about the safe and effective use of KAZANO

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take KAZANO for a condition for which it was not prescribed. Do not give KAZANO to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about KAZANO. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about KAZANO that is written for health professionals.

For more information go to www.kazano.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in KAZANO?

Active ingredients: alogliptin and metformin hydrochloride

Inactive ingredients: mannitol, microcrystalline cellulose, povidone, crospovidone and magnesium stearate; the tablets are film-coated with hypromellose 2910, talc, titanium dioxide and ferric oxide yellow.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

2/2017

EXHIBIT 7

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OSENI safely and effectively. See full prescribing information for OSENI.

OSENI (alogliptin and pioglitazone) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: CONGESTIVE HEART FAILURE

See full prescribing information for complete boxed warning

- Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. (5.1)
- After initiation of OSENI and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in OSENI must be considered. (5.1)
- OSENI is not recommended in patients with symptomatic heart failure. (5.1)
- Initiation of OSENI in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. (4, 5.1)

INDICATIONS AND USAGE

OSENI is a dipeptidyl peptidase-4 inhibitor and thiazolidinedione combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

Important Limitations of Use: Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose of OSENI based on the patient's current regimen and concurrent medical condition but do not exceed a daily dose of alogliptin 25 mg and pioglitazone 45 mg. (2.1)
- Can be taken with or without food. (2.1)
- Limit initial dose of pioglitazone to 15 mg once daily in patients with NYHA Class I or II heart failure. (2.1)
- Adjust dose if moderate renal impairment. (2.2)

Degree of Renal Impairment	Creatinine Clearance (mL/min)	Recommended Dosing
Moderate	≥30 to <60	12.5 mg/15 mg, 12.5 mg/30 mg or 12.5 mg/45 mg once daily

- OSENI is not recommended for patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis. (2.2)
- The maximum recommended dose of pioglitazone is 15 mg once daily in patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil). (2.3, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

25 mg alogliptin and 15 mg pioglitazone, 25 mg alogliptin and 30 mg pioglitazone, 25 mg alogliptin and 45 mg pioglitazone. (3)

12.5 mg alogliptin and 15 mg pioglitazone, 12.5 mg alogliptin and 30 mg pioglitazone, 12.5 mg alogliptin and 45 mg pioglitazone. (3)

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to alogliptin or pioglitazone, components of OSENI, such as anaphylaxis, angioedema or severe cutaneous adverse reactions. (4)
- Do not initiate OSENI in patients with established NYHA Class III or IV heart failure. (4)

WARNINGS AND PRECAUTIONS

- Congestive heart failure: Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Consider the risks and benefits of OSENI prior to

initiating treatment in patients at risk for heart failure. Monitor patients at risk for heart failure for signs and symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of OSENI. (5.1)

- Acute pancreatitis: There have been postmarketing reports of acute pancreatitis. If pancreatitis is suspected, promptly discontinue OSENI. (5.2)
- Hypersensitivity: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin such as anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. In such cases, promptly discontinue OSENI, assess for other potential causes, institute appropriate monitoring and treatment and initiate alternative treatment for diabetes. (5.3)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt OSENI and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart OSENI if liver injury is confirmed and no alternative etiology can be found. Use with caution in patients with liver disease. (5.4)
- Edema: Dose-related edema may occur. (5.5)
- Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health. (5.6)
- Bladder cancer: May increase the risk of bladder cancer. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer. (5.7)
- Hypoglycemia: When an insulin secretagogue (e.g., sulfonylurea) or insulin is used in combination with OSENI, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.8)
- Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes according to current standards of care with prompt evaluation for acute visual changes. (5.9)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate. (5.10)
- Bullous pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue OSENI. (5.11)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with OSENI. (5.12)

ADVERSE REACTIONS

The most common adverse reactions (4% or greater incidence) are nasopharyngitis, back pain and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) increase pioglitazone concentrations. Limit the pioglitazone dose to 15 mg daily. (2.3, 7.1)
- CYP2C8 inducers (e.g., rifampin) may decrease pioglitazone concentrations. (7.2)
- Topiramate may decrease pioglitazone concentrations. (7.3)

USE IN SPECIFIC POPULATIONS

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2019

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE

- Thiazolidinediones, including pioglitazone, which is a component of OSENI, cause or exacerbate congestive heart failure in some patients [see *Warnings and Precautions (5.1)*].
- After initiation of OSENI and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in OSENI must be considered [see *Warnings and Precautions (5.1)*].
- OSENI is not recommended in patients with symptomatic heart failure [see *Warnings and Precautions (5.1)*].
- Initiation of OSENI in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

OSENI is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and pioglitazone is appropriate [see *Clinical Studies (14)*].

Important Limitations of Use

OSENI is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

OSENI should be taken once daily and can be taken with or without food. The tablets must not be split before swallowing.

The recommended starting dose for OSENI (alogliptin and pioglitazone):

- for patients inadequately controlled on diet and exercise is 25 mg/15 mg or 25 mg/30 mg,
- for patients inadequately controlled on metformin monotherapy is 25 mg/15 mg or 25 mg/30 mg,
- for patients on alogliptin who require additional glycemic control is 25 mg/15 mg or 25 mg/30 mg,
- for patients on pioglitazone who require additional glycemic control is 25 mg/15 mg, 25 mg/30 mg or 25 mg/45 mg as appropriate based upon current therapy,
- for patients switching from alogliptin coadministered with pioglitazone, OSENI may be initiated at the dose of alogliptin and pioglitazone based upon current therapy,
- for patients with congestive heart failure (NYHA Class I or II) is 25 mg/15 mg.

The OSENI dose can be titrated up to a maximum of 25 mg/45 mg once daily based on glycemic response as determined by hemoglobin A1c (A1C).

After initiation of OSENI or with dose increase, monitor patients carefully for adverse reactions related to fluid retention as has been seen with pioglitazone (e.g., weight gain, edema and signs and symptoms of congestive heart failure) [see *Boxed Warning and Warnings and Precautions (5.1)*].

2.2 Patients with Renal Impairment

No dose adjustment of OSENI is necessary for patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 mL/min).

The dose of OSENI is 12.5 mg/15 mg, 12.5 mg/30 mg or 12.5 mg/45 mg once daily for patients with moderate renal impairment (CrCl ≥ 30 to < 60 mL/min).

OSENI is not recommended for patients with severe renal impairment or ESRD [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. Coadministration of pioglitazone and alogliptin 6.25 mg once daily based on individual requirements may be considered in these patients.

Because there is a need for dose adjustment based upon renal function, assessment of renal function is recommended prior to initiation of OSENI therapy and periodically thereafter.

2.3 Coadministration with Strong CYP2C8 Inhibitors

Coadministration of pioglitazone and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately three-fold. Therefore, the maximum recommended dose of OSENI is 25 mg/15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

- 25 mg/15 mg tablets are yellow, round, biconvex, and film-coated, with both “A/P” and “25/15” printed on one side.
- 25 mg/30 mg tablets are peach, round, biconvex, and film-coated, with both “A/P” and “25/30” printed on one side.
- 25 mg/45 mg tablets are red, round, biconvex, and film-coated, with both “A/P” and “25/45” printed on one side.
- 12.5 mg/15 mg tablets are pale yellow, round, biconvex, and film-coated, with both “A/P” and “12.5/15” printed on one side.
- 12.5 mg/30 mg tablets are pale peach, round, biconvex, and film-coated, with both “A/P” and “12.5/30” printed on one side.
- 12.5 mg/45 mg tablets are pale red, round, biconvex, and film-coated, with both “A/P” and “12.5/45” printed on one side.

4 CONTRAINDICATIONS

History of a serious hypersensitivity reaction to alogliptin or pioglitazone, components of OSENI, such as anaphylaxis, angioedema or severe cutaneous adverse reactions.

Do not initiate in patients with NYHA Class III or IV heart failure [see *Boxed Warning*].

5 WARNINGS AND PRECAUTIONS

5.1 Congestive Heart Failure

Consider the risks and benefits of OSENI prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of congestive heart failure. Patients should be advised of the characteristic symptoms of congestive heart failure and should be instructed to immediately report such symptoms. If congestive heart failure develops, it should be managed according to current standards of care and consider discontinuation of OSENI.

Alogliptin

In the EXAMINE trial which enrolled patients with type 2 diabetes and recent acute coronary syndrome, 106 (3.9%) of patients treated with alogliptin and 89 (3.3%) of patients treated with placebo were hospitalized for congestive heart failure.

Pioglitazone

Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic medications and is most common when pioglitazone is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure [see *Boxed Warning, Contraindications (4) and Adverse Reactions (6.1)*].

5.2 Pancreatitis

Acute pancreatitis has been reported in the postmarketing setting and in randomized clinical trials. In glycemic control trials in patients with type 2 diabetes, acute pancreatitis was reported in six (0.2%) patients treated with alogliptin 25 mg and two (<0.1%) patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), acute pancreatitis was reported in ten (0.4%) patients treated with alogliptin and in seven (0.3%) patients treated with placebo.

It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using OSENI.

After initiation of OSENI, patients should be observed for signs and symptoms of pancreatitis. If pancreatitis is suspected, OSENI should promptly be discontinued and appropriate management should be initiated.

5.3 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin. These reactions include anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. If a serious hypersensitivity reaction is suspected, discontinue OSENI, assess for other potential causes for the event and institute alternative treatment for diabetes [see *Adverse Reactions (6.3)*]. Use caution in patients with a history of angioedema with another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with OSENI.

5.4 Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking pioglitazone or alogliptin, although some of the reports contain insufficient information necessary to establish the probable cause [see *Adverse Reactions (6.3)*].

In glycemic control trials of alogliptin in patients with type 2 diabetes, serum alanine aminotransferase (ALT) elevations greater than three times the upper limit of normal (ULN) were reported in 1.3% of patients treated with alogliptin 25 mg and 1.7% of patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), increases in serum alanine aminotransferase three times the upper limit of the reference range occurred in 2.4% of patients treated with alogliptin and in 1.8% of patients treated with placebo.

Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (ALT, aspartate aminotransferase [AST], alkaline phosphatase and total bilirubin) and assessing the patient is recommended before initiating OSENI therapy. In patients with abnormal liver tests, OSENI should be initiated with caution.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), OSENI treatment should be interrupted and an investigation done to establish the probable cause. OSENI should not be restarted in these patients without another explanation for the liver test abnormalities.

5.5 Edema

Pioglitazone

In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related [see *Adverse Reactions (6.1)*]. In postmarketing experience, reports of new onset or worsening of edema have been received.

OSENI should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, OSENI should be used with caution in patients at risk for congestive heart failure. Patients treated with OSENI should be monitored for signs and symptoms of congestive heart failure [see *Boxed Warning, Warnings and Precautions (5.1) and Patient Counseling Information (17)*].

5.6 Fractures

Pioglitazone

In PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events), 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and persisted during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in the incidence of fracture was observed in men treated with pioglitazone (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.

5.7 Urinary Bladder Tumors

Pioglitazone

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study [see *Nonclinical Toxicology (13.1)*]. In addition, during the three year PROactive clinical trial, 14 patients out of 2605 (0.54%) randomized to pioglitazone and 5 out of 2633 (0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.23%) cases on pioglitazone and two (0.08%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR =1.00; [95% CI: 0.59–1.72]).

Findings regarding the risk of bladder cancer in patients exposed to pioglitazone vary among observational studies; some did not find an increased risk of bladder cancer associated with pioglitazone, while others did.

A large prospective 10 year observational cohort study conducted in the United States found no statistically significant increase in the risk of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone (HR =1.06 [95% CI 0.89–1.26]).

A retrospective cohort study conducted with data from the United Kingdom found a statistically significant association between ever exposure to pioglitazone and bladder cancer (HR: 1.63; [95% CI: 1.22–2.19]).

Associations between cumulative dose or cumulative duration of exposure to pioglitazone and bladder cancer were not detected in some studies including the 10 year observational study in the U.S., but were in others. Inconsistent findings and limitations inherent in these and other studies preclude conclusive interpretations of the observational data.

Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors.

Consequently, OSENI should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with OSENI should be considered in patients with a prior history of bladder cancer.

5.8 Use with Medications Known to Cause Hypoglycemia

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with OSENI.

5.9 Macular Edema

Pioglitazone

Macular edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but others were diagnosed on routine ophthalmologic examination.

Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione.

Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings [see *Adverse Reactions (6.1)*].

5.10 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.11 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving OSENI. If bullous pemphigoid is suspected, OSENI should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.12 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with OSENI.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Congestive Heart Failure [see *Warnings and Precautions (5.1)*]
- Pancreatitis [see *Warnings and Precautions (5.2)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.3)*]
- Hepatic Effects [see *Warnings and Precautions (5.4)*]
- Severe and Disabling Arthralgia [see *Warnings and Precautions (5.10)*]
- Bullous Pemphigoid [see *Warnings and Precautions (5.11)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Alogliptin and Pioglitazone

Over 1500 patients with type 2 diabetes have received alogliptin coadministered with pioglitazone in four large, randomized, double-blind, controlled clinical trials. The mean exposure to OSENI was 29 weeks with more than 100 subjects treated for more than one year. The studies consisted of two placebo-controlled studies of 16 to 26 weeks in duration and two active-controlled studies of 26 weeks and 52 weeks in duration. In the OSENI arm, the mean duration of diabetes was approximately six years, the mean body mass index (BMI) was 31 kg/m² (54% of patients had a BMI ≥30 kg/m²), and the mean age was 54 years (16% of patients ≥65 years of age).

In a pooled analysis of these four controlled clinical studies, the overall incidence of adverse reactions was 65% in patients treated with OSENI compared to 57% treated with placebo. Overall discontinuation of therapy due to adverse reactions was 2.5% with OSENI compared to 2.0% with placebo, 3.7% with pioglitazone or 1.3% with alogliptin.

Adverse reactions reported in ≥4% of patients treated with OSENI and more frequently than in patients who received alogliptin, pioglitazone or placebo are summarized in *Table 1*.

Table 1. Adverse Reactions Reported in ≥4% of Patients Treated with OSENI and More Frequently than in Patients Receiving Either Alogliptin, Pioglitazone or Placebo

	Number of Patients (%)			
	OSENI*	Alogliptin†	Pioglitazone‡	Placebo
	N=1533	N=446	N=949	N=153
Nasopharyngitis	75 (4.9)	21 (4.7)	37 (3.9)	6 (3.9)
Back Pain	64 (4.2)	9 (2.0)	32 (3.4)	5 (3.3)
Upper Respiratory Tract Infection	63 (4.1)	19 (4.3)	26 (2.7)	5 (3.3)

*OSENI – includes data pooled for patients receiving alogliptin 25 mg and 12.5 mg combined with pioglitazone 15 mg, 30 mg and 45 mg

†Alogliptin – includes data pooled for patients receiving alogliptin 25 mg and 12.5 mg

‡Pioglitazone – includes data pooled for patients receiving pioglitazone 15 mg, 30 mg and 45 mg

Alogliptin Add-On Therapy to a Thiazolidinedione

In addition, in a 26 week, placebo-controlled, double-blind study, patients inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea were treated with add-on alogliptin therapy or placebo; the adverse reactions reported in ≥5% of patients and more frequently than in patients who received placebo was influenza (alogliptin, 5.5%; placebo, 4.1%).

Hypoglycemia

In a 26 week, placebo-controlled factorial study with alogliptin in combination with pioglitazone on background therapy with metformin, the incidence of subjects reporting hypoglycemia was 0.8%, 0% and 3.8% for alogliptin 25 mg with pioglitazone 15 mg, 30 mg or 45 mg, respectively; 2.3% for alogliptin 25 mg; 4.7%, 0.8% and 0.8% for pioglitazone 15 mg, 30 mg or 45 mg, respectively; and 0.8% for placebo.

In a 26 week, active-controlled, double-blind study with alogliptin alone, pioglitazone alone or alogliptin coadministered with pioglitazone in patients inadequately controlled on diet and exercise, the incidence of hypoglycemia was 3% on alogliptin 25 mg with pioglitazone 30 mg, 0.6% on alogliptin 25 mg and 1.8% on pioglitazone 30 mg.

In a 52 week, active-controlled, double-blind study of alogliptin as add-on therapy to the combination of pioglitazone 30 mg and metformin compared to the titration of pioglitazone 30 mg to 45 mg and metformin, the incidence of subjects reporting hypoglycemia was 4.5% in the alogliptin 25 mg with pioglitazone 30 mg and metformin group versus 1.5% in the pioglitazone 45 mg and metformin group.

Alogliptin

A total of 14,778 patients with type 2 diabetes participated in 14 randomized, double-blind, controlled clinical trials of whom 9052 subjects were treated with alogliptin, 3469 subjects were treated with placebo and 2257 were treated with an active comparator. The mean duration of diabetes was seven years, the mean body mass index (BMI) was 31 kg/m² (49% of patients had a BMI ≥30 kg/m²) and the mean age was 58 years (26% of patients ≥65 years of age).

The mean exposure to alogliptin was 49 weeks with 3348 subjects treated for more than one year.

In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse reactions was 73% in patients treated with alogliptin 25 mg compared to 75% with placebo and 70% with active

comparator. Overall discontinuation of therapy due to adverse reactions was 6.8% with alogliptin 25 mg compared to 8.4% with placebo or 6.2% with active comparator.

Adverse reactions reported in $\geq 4\%$ of patients treated with alogliptin 25 mg and more frequently than in patients who received placebo are summarized in *Table 2*.

Table 2. Adverse Reactions Reported in $\geq 4\%$ Patients Treated with Alogliptin 25 mg and More Frequently than in Patients Given Placebo in Pooled Studies

	Number of Patients (%)		
	Alogliptin 25 mg	Placebo	Active Comparator
	N=6447	N=3469	N=2257
Nasopharyngitis	309 (4.8)	152 (4.4)	113 (5.0)
Upper Respiratory Tract Infection	287 (4.5)	121 (3.5)	113 (5.0)
Headache	278 (4.3)	101 (2.9)	121 (5.4)

Hypoglycemia

Hypoglycemic events were documented based upon a blood glucose value and/or clinical signs and symptoms of hypoglycemia.

In the monotherapy study, the incidence of hypoglycemia was 1.5% in patients treated with alogliptin compared to 1.6% with placebo. The use of alogliptin as add-on therapy to glyburide or insulin did not increase the incidence of hypoglycemia compared to placebo. In a monotherapy study comparing alogliptin to a sulfonylurea in elderly patients, the incidence of hypoglycemia was 5.4% with alogliptin compared to 26% with glipizide.

In the EXAMINE trial, the incidence of investigator reported hypoglycemia was 6.7% in patients receiving alogliptin and 6.5% in patients receiving placebo. Serious adverse reactions of hypoglycemia were reported in 0.8% of patients treated with alogliptin and in 0.6% of patients treated with placebo.

Renal Impairment

In glycemic control trials in patients with type 2 diabetes, 3.4% of patients treated with alogliptin and 1.3% of patients treated with placebo had renal function adverse reactions. The most commonly reported adverse reactions were renal impairment (0.5% for alogliptin and 0.1% for active comparators or placebo), decreased creatinine clearance (1.6% for alogliptin and 0.5% for active comparators or placebo) and increased blood creatinine (0.5% for alogliptin and 0.3% for active comparators or placebo) [see *Use in Specific Populations (8.6)*].

In the EXAMINE trial of high CV risk type 2 diabetes patients, 23% of patients treated with alogliptin and 21% of patients treated with placebo had an investigator reported renal impairment adverse reaction. The most commonly reported adverse reactions were renal impairment (7.7% for alogliptin and 6.7% for placebo), decreased glomerular filtration rate (4.9% for alogliptin and 4.3% for placebo) and decreased renal clearance (2.2% for alogliptin and 1.8% for placebo). Laboratory measures of renal function were also assessed. Estimated glomerular filtration rate decreased by 25% or more in 21.1% of patients treated with alogliptin and 18.7% of patients treated with placebo. Worsening of chronic kidney disease stage was seen in 16.8% of patients treated with alogliptin and in 15.5% of patients treated with placebo.

Pioglitazone

Over 8500 patients with type 2 diabetes have been treated with pioglitazone in randomized, double-blind, controlled clinical trials, including 2605 patients with type 2 diabetes and macrovascular disease treated with pioglitazone in the PROactive clinical trial. In these trials, over 6000 patients have been treated with pioglitazone for six months or longer, over 4500 patients have been treated with pioglitazone for one year or longer, and over 3000 patients have been treated with pioglitazone for at least two years.

Common Adverse Reactions: 16 to 26 Week Monotherapy Trials

A summary of the incidence and type of common adverse reactions reported in three pooled 16 to 26 week placebo-controlled monotherapy trials of pioglitazone is provided in *Table 3*. Terms that are reported represent those that occurred at an incidence of >5% and more commonly in patients treated with pioglitazone than in patients who received placebo. None of these adverse reactions were related to pioglitazone dose.

Table 3. Three Pooled 16 to 26 Week Placebo-Controlled Clinical Trials of Pioglitazone Monotherapy: Adverse Reactions Reported at an Incidence >5% and More Commonly in Patients Treated with Pioglitazone than in Patients Treated with Placebo

% of Patients		
	Placebo N=259	Pioglitazone N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Pharyngitis	0.8	5.1

Congestive Heart Failure

A summary of the incidence of adverse reactions related to congestive heart failure for the 16 to 24 week add-on to sulfonylurea trials, for the 16 to 24 week add-on to insulin trials, and for the 16 to 24 week add-on to metformin trials were (at least one congestive heart failure, 0.2% to 1.7%; hospitalized due to congestive heart failure, 0.2% to 0.9%). None of the reactions were fatal.

Patients with type 2 diabetes and NYHA class II or early class III congestive heart failure were randomized to receive 24 weeks of double-blind treatment with either pioglitazone at daily doses of 30 mg to 45 mg (N=262) or glyburide at daily doses of 10 mg to 15 mg (N=256). A summary of the incidence of adverse reactions related to congestive heart failure reported in this study is provided in *Table 4*.

Table 4. Treatment-Emergent Adverse Reactions of Congestive Heart Failure (CHF) in Patients with NYHA Class II or III Congestive Heart Failure Treated with Pioglitazone or Glyburide

	Number (%) of Subjects	
	Pioglitazone N=262	Glyburide N=256
Death due to cardiovascular causes (adjudicated)	5 (1.9%)	6 (2.3%)
Overnight hospitalization for worsening CHF (adjudicated)	26 (9.9%)	12 (4.7%)
Emergency room visit for CHF (adjudicated)	4 (1.5%)	3 (1.2%)
Patients experiencing CHF progression during study	35 (13.4%)	21 (8.2%)

Congestive heart failure events leading to hospitalization that occurred during the PROactive trial are summarized in *Table 5*.

Table 5. Treatment-Emergent Adverse Reactions of Congestive Heart Failure (CHF) in PROactive Trial

	Number (%) of Patients	
	Placebo N=2633	Pioglitazone N=2605
At least one hospitalized congestive heart failure event	108 (4.1%)	149 (5.7%)
Fatal	22 (0.8%)	25 (1%)
Hospitalized, nonfatal	86 (3.3%)	124 (4.7%)

Cardiovascular Safety

In the PROactive trial, 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. Almost all patients (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrates, diuretics, aspirin, statins and fibrates). At baseline, patients had a mean age of 62 years, mean duration of diabetes of 9.5 years and mean A1C of 8.1%. Mean duration of follow-up was 34.5 months.

The primary objective of this trial was to examine the effect of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in a cardiovascular composite endpoint that included all-cause mortality, nonfatal myocardial infarction (MI) including silent MI, stroke, acute coronary syndrome, cardiac intervention including coronary artery bypass grafting or percutaneous intervention, major leg amputation above the ankle

and bypass surgery or revascularization in the leg. A total of 514 (19.7%) patients treated with pioglitazone and 572 (21.7%) placebo-treated patients experienced at least one event from the primary composite endpoint (hazard ratio 0.90; 95% Confidence Interval: 0.80, 1.02; p=0.10).

Although there was no statistically significant difference between pioglitazone and placebo for the three-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with pioglitazone. The number of first occurrences and total individual events contributing to the primary composite endpoint is shown in *Table 6*.

Table 6. PROactive: Number of First and Total Events for Each Component Within the Cardiovascular Composite Endpoint

Cardiovascular Events	Placebo N=2633		Pioglitazone N=2605	
	First Events n (%)	Total Events n	First Events n (%)	Total Events n
Any Event	572 (21.7)	900	514 (19.7)	803
All-Cause Mortality	122 (4.6)	186	110 (4.2)	177
Nonfatal Myocardial Infarction (MI)	118 (4.5)	157	105 (4)	131
Stroke	96 (3.6)	119	76 (2.9)	92
Acute Coronary Syndrome	63 (2.4)	78	42 (1.6)	65
Cardiac Intervention (CABG/PCI)	101 (3.8)	240	101 (3.9)	195
Major Leg Amputation	15 (0.6)	28	9 (0.3)	28
Leg Revascularization	57 (2.2)	92	71 (2.7)	115

CABG=coronary artery bypass grafting; PCI=percutaneous intervention

Weight Gain

Dose-related weight gain occurs when pioglitazone is used alone or in combination with other antidiabetic medications. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Edema

Edema induced from taking pioglitazone is reversible when pioglitazone is discontinued. The edema usually does not require hospitalization unless there is coexisting congestive heart failure.

Hepatic Effects

There has been no evidence of pioglitazone-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date. One randomized, double-blind, three-year trial comparing pioglitazone to glyburide as add-on to metformin and insulin therapy was specifically designed to evaluate the incidence of serum ALT elevation to greater than three times the upper limit of the reference range, measured every eight weeks for the first 48 weeks of the trial then every 12 weeks thereafter. A total of 3/1051 (0.3%) patients treated with pioglitazone and 9/1046 (0.9%) patients treated with glyburide developed ALT values greater than three times the upper limit of the reference range. None of the patients treated with pioglitazone in the pioglitazone controlled clinical trial database to date have had

a serum ALT greater than three times the upper limit of the reference range and a corresponding total bilirubin greater than two times the upper limit of the reference range, a combination predictive of the potential for severe drug-induced liver injury.

Hypoglycemia

In the pioglitazone clinical trials, adverse reactions of hypoglycemia were reported based on clinical judgment of the investigators and did not require confirmation with finger stick glucose testing. In the 16 week add-on to sulfonylurea trial, the incidence of reported hypoglycemia was 3.7% with pioglitazone 30 mg and 0.5% with placebo. In the 16 week add-on to insulin trial, the incidence of reported hypoglycemia was 7.9% with pioglitazone 15 mg, 15.4% with pioglitazone 30 mg and 4.8% with placebo. The incidence of reported hypoglycemia was higher with pioglitazone 45 mg compared to pioglitazone 30 mg in both the 24 week add-on to sulfonylurea trial (15.7% versus 13.4%) and in the 24 week add-on to insulin trial (47.8% versus 43.5%). Three patients in these four trials were hospitalized due to hypoglycemia. All three patients were receiving pioglitazone 30 mg (0.9%) in the 24 week add-on to insulin trial. An additional 14 patients reported severe hypoglycemia (defined as causing considerable interference with patient's usual activities) that did not require hospitalization. These patients were receiving pioglitazone 45 mg in combination with sulfonylurea (N=2) or pioglitazone 30 mg or 45 mg in combination with insulin (N=12).

Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study [see *Nonclinical Toxicology (13.1)*]. During the three year PROactive clinical trial, 14 patients out of 2605 (0.54%) randomized to pioglitazone and 5 out of 2633 (0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.23%) cases on pioglitazone and two (0.08%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR =1.00; 95% CI: 0.59-1.72) [see *Warnings and Precautions (5.7)*].

6.2 Laboratory Abnormalities

Pioglitazone

Hematologic Effects

Pioglitazone may cause decreases in hemoglobin and hematocrit. In placebo-controlled monotherapy trials, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone compared with a mean change in hemoglobin of -1% to +1% in placebo-treated patients. These changes primarily occurred within the first four to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and are not likely to be associated with any clinically significant hematologic effects.

Creatine Phosphokinase

During protocol-specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in nine (0.2%) patients treated with pioglitazone (values of 2150 to 11400 IU/L) and in no comparator-treated patients. Six of these nine patients continued to receive pioglitazone, two patients were noted to have the CPK elevation on the last day of dosing and one patient discontinued pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

6.3 Postmarketing Experience

Alogliptin

The following adverse reactions have been identified during the postmarketing use of alogliptin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Acute pancreatitis, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and severe cutaneous adverse reactions, including Stevens-Johnson syndrome, hepatic enzyme elevations, fulminant hepatic failure, severe and disabling arthralgia and bullous pemphigoid, rhabdomyolysis, diarrhea, constipation, nausea and ileus [see *Warnings and Precautions* (5.2, 5.3, 5.4, 5.10, 5.11)].

Pioglitazone

The following adverse reactions have been identified during the postmarketing use of pioglitazone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

New onset or worsening diabetic macular edema with decreased visual acuity [see *Warnings and Precautions* (5.9)].

Fatal and nonfatal hepatic failure [see *Warnings and Precautions* (5.4)].

Postmarketing reports of congestive heart failure have been reported in patients treated with pioglitazone, both with and without previously known heart disease and both with and without concomitant insulin administration.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure [see *Boxed Warning and Warnings and Precautions* (5.1)].

7 DRUG INTERACTIONS

Alogliptin

Alogliptin is primarily renally excreted. Cytochrome (CYP) P450-related metabolism is negligible. No significant drug-drug interactions were observed with the CYP-substrates or inhibitors tested or with renally excreted drugs [see *Clinical Pharmacology* (12.3)].

7.1 Strong CYP2C8 Inhibitors

Pioglitazone

An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the concentration-time curve [AUC]) and half-life of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3)].

7.2 CYP2C8 Inducers

Pioglitazone

An inducer of CYP2C8 (e.g., rifampin) may significantly decrease the exposure (AUC) of pioglitazone. Therefore, if an inducer of CYP2C8 is started or stopped during treatment with OSENI, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dose of 45 mg for pioglitazone [see *Clinical Pharmacology* (12.3)].

7.3 Topiramate

Pioglitazone

A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone and topiramate [see *Clinical Pharmacology* (12.3)]. The clinical relevance of this decrease is unknown; however, when OSENI and topiramate are used concomitantly, monitor patients for adequate glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with OSENI in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

In animal reproduction studies, no adverse developmental effects were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis at exposures up to 5 and 35 times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were observed when alogliptin was administered to pregnant rats and rabbits during organogenesis at exposures 180 and 149 times the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC) [see *Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

Alogliptin and Pioglitazone

Co-administration of 100 mg/kg alogliptin and 40 mg/kg pioglitazone (39 and 10 times the 25 mg and 45 mg clinical doses, respectively, based on body surface area) to pregnant rats during organogenesis slightly augmented pioglitazone-related fetal effects of delayed development and reduced fetal weights but did not result in embryofetal mortality or teratogenicity.

Alogliptin

Alogliptin administered to pregnant rabbits and rats during the period of organogenesis did not cause adverse developmental effects at doses of up to 200 mg/kg and 500 mg/kg, or 149 times and 180 times, the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC). Placental transfer of alogliptin into the fetus was observed following oral dosing to pregnant rats.

No adverse developmental outcomes were observed in offspring when alogliptin was administered to pregnant rats during gestation and lactation at doses up to 250 mg/kg (~95 times the 25 mg clinical dose, based on AUC).

Pioglitazone

Pioglitazone administered to pregnant rats during organogenesis did not cause adverse developmental effects at a dose of 20 mg/kg (~5-times the 45 mg clinical dose), but delayed parturition and reduced embryofetal viability at 40 and 80 mg/kg, or ≥9-times the 45 mg clinical dose, by body surface area. In pregnant rabbits administered pioglitazone during organogenesis, no adverse developmental effects were observed at 80 mg/kg (~35-times the 45 mg clinical dose), but reduced embryofetal viability at 160 mg/kg, or ~69-times the 45 mg clinical dose, by body surface area. When pregnant rats received pioglitazone during late gestation and lactation, delayed postnatal development, attributed to decreased body weight, occurred in offspring at maternal doses of 10 mg/kg and above or ≥2 times the 45 mg clinical dose, by body surface area.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pioglitazone or alogliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Pioglitazone and alogliptin are present in rat milk; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OSENI and any potential adverse effects on the breastfed infant from OSENI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of OSENI in pediatric patients have not been established.

OSENI is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures and urinary bladder tumors [see *Warnings and Precautions (5.1, 5.5, 5.6, 5.7)*].

8.5 Geriatric Use

Alogliptin and Pioglitazone

Of the total number of patients (N=1533) in clinical safety and efficacy studies treated with alogliptin and pioglitazone, 248 (16.2%) patients were 65 years and older and 15 (1%) patients were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this and other reported clinical experiences have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be excluded.

Alogliptin

Of the total number of patients (N=9052) in clinical safety and efficacy studies treated with alogliptin, 2257 (24.9%) patients were ≥65 years old and 386 (4.3%) patients were ≥75 years old. No overall differences in safety or effectiveness were observed between patients ≥65 years old and younger patients.

Pioglitazone

A total of 92 patients (15.2%) treated with pioglitazone in the three pooled, 16 to 26 week, double-blind, placebo-controlled, monotherapy trials were ≥65 years old and two patients (0.3%) were ≥75 years old. In the two pooled 16 to 24 week add-on to sulfonylurea trials, 201 patients (18.7%) treated with pioglitazone were ≥65 years old and 19 (1.8%) were ≥75 years old. In the two pooled 16 to 24 week add-on to metformin trials, 155 patients (15.5%) treated with pioglitazone were ≥65 years old

and 19 (1.9%) were ≥ 75 years old. In the two pooled 16 to 24 week add-on to insulin trials, 272 patients (25.4%) treated with pioglitazone were ≥ 65 years old and 22 (2.1%) were ≥ 75 years old. In PROactive, 1068 patients (41%) treated with pioglitazone were ≥ 65 years old and 42 (1.6%) were ≥ 75 years old.

In pharmacokinetic studies with pioglitazone, no significant differences were observed in pharmacokinetic parameters between elderly and younger patients. These clinical experiences have not identified differences in effectiveness and safety between the elderly (≥ 65 years) and younger patients although small sample sizes for patients ≥ 75 years old limit conclusions [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

Alogliptin

A total of 602 patients with moderate renal impairment (eGFR ≥ 30 and <60 mL/min/1.73 m²) and four patients with severe renal impairment/end-stage renal disease (eGFR <30 mL/min/1.73 m² or <15 mL/min/1.73 m², respectively) at baseline were treated with alogliptin in clinical trials in patients with type 2 diabetes. Reductions in HbA1c were generally similar in this subgroup of patients. The overall incidence of adverse reactions was generally balanced between alogliptin and placebo treatments in this subgroup of patients.

In the EXAMINE trial of high CV risk type 2 diabetes patients, 694 patients had moderate renal impairment and 78 patients had severe renal impairment or end-stage renal disease at baseline. The overall incidences of adverse reactions, serious adverse reactions and adverse reactions leading to study drug discontinuation were generally similar between the treatment groups.

8.7 Hepatic Impairment

Alogliptin

No dose adjustments are required in patients with mild to moderate hepatic impairment (Child-Pugh Grade A and B) based on insignificant change in systemic exposures (e.g., AUC) compared to subjects with normal hepatic function in a pharmacokinetic study. Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh Grade C). Use caution when administering alogliptin to patients with liver disease [see *Warnings and Precautions* (5.4)].

Pioglitazone

No dose adjustments are required in patients with hepatic impairment (Child-Pugh Grade B and C) based on insignificant change in systemic exposures (e.g., AUC) compared to subjects with normal hepatic function in a pharmacokinetic study. However, use with caution in patients with liver disease [see *Warnings and Precautions* (5.4)].

10 OVERDOSAGE

Alogliptin

The highest doses of alogliptin administered in clinical trials were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes (equivalent to 32 times and 16 times the maximum recommended clinical dose of 25 mg, respectively). No serious adverse reactions were observed at these doses.

In the event of an overdose, it is reasonable to institute the necessary clinical monitoring and supportive therapy as dictated by the patient's clinical status. Per clinical judgment, it may be reasonable to initiate removal of unabsorbed material from the gastrointestinal tract.

Alogliptin is minimally dialyzable; over a three-hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to be beneficial in an overdose situation. It is not known if alogliptin is dialyzable by peritoneal dialysis.

Pioglitazone

During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

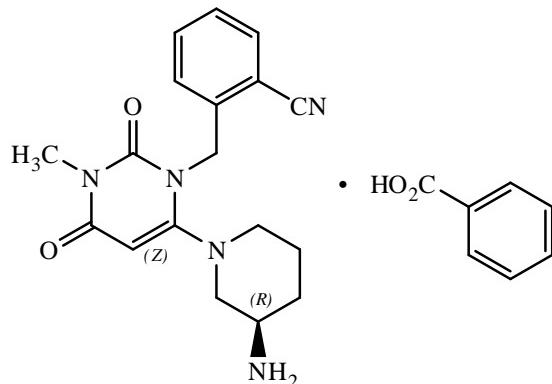
In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

11 DESCRIPTION

OSENI tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: alogliptin and pioglitazone.

Alogliptin

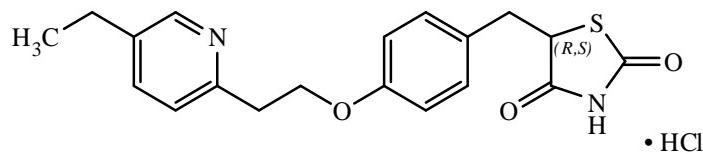
Alogliptin is a selective, orally bioavailable inhibitor of the enzymatic activity of dipeptidyl peptidase-4 (DPP-4). Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-(6-[{(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile monobenzoate. It has a molecular formula of $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$ and a molecular weight of 461.51 daltons. The structural formula is:



Alogliptin benzoate is a white to off-white crystalline powder containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol and very slightly soluble in octanol and isopropyl acetate.

Pioglitazone

Pioglitazone is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance. Chemically, pioglitazone is prepared as hydrochloride salt, which is identified as (\pm) -5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride. It has a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$ and a molecular weight of 392.90 daltons. The structural formula is:



Pioglitazone hydrochloride is an odorless white crystalline powder that contains one asymmetric carbon in the thiazolidinedione moiety. The synthetic compound is a racemate and the two enantiomers of pioglitazone interconvert *in vivo*. It is soluble in *N,N* dimethylformamide, slightly

soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water and insoluble in ether.

OSENI is available as a fixed-dose combination tablet for oral administration containing 34 mg alogliptin benzoate equivalent to 25 mg alogliptin and any of the following strengths of pioglitazone hydrochloride:

- 16.53 mg pioglitazone hydrochloride equivalent to 15 mg pioglitazone (25 mg/15 mg)
- 33.06 mg pioglitazone hydrochloride equivalent to 30 mg pioglitazone (25 mg/30 mg)
- 49.59 mg pioglitazone hydrochloride equivalent to 45 mg pioglitazone (25 mg/45 mg)

OSENI is also available as a fixed-dose combination tablet for oral administration containing 17 mg alogliptin benzoate equivalent to 12.5 mg alogliptin and any of the following strengths of pioglitazone hydrochloride:

- 16.53 mg pioglitazone hydrochloride equivalent to 15 mg pioglitazone (12.5 mg/15 mg)
- 33.06 mg pioglitazone hydrochloride equivalent to 30 mg pioglitazone (12.5 mg/30 mg)
- 49.59 mg pioglitazone hydrochloride equivalent to 45 mg pioglitazone (12.5 mg/45 mg)

OSENI tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate and lactose monohydrate; the tablets are film-coated with hypromellose, polyethylene glycol, titanium dioxide, talc and ferric oxide (yellow and/or red) and are marked with printing ink (Red A1 or Gray F1).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

OSENI combines two antihyperglycemic agents with complementary and distinct mechanisms of action to improve glycemic control in patients with type 2 diabetes: alogliptin, a selective inhibitor of DPP-4, and pioglitazone, a member of the TZD class.

Alogliptin

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Pioglitazone

Pharmacologic studies indicate that pioglitazone improves insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPAR γ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle and liver. Activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin- responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

12.2 Pharmacodynamics

Alogliptin and Pioglitazone

In a 26 week, randomized, active-controlled study, patients with type 2 diabetes received alogliptin 25 mg coadministered with pioglitazone 30 mg, alogliptin 12.5 mg coadministered with pioglitazone 30 mg, alogliptin 25 mg alone or pioglitazone 30 mg alone. Patients who were randomized to alogliptin 25 mg with pioglitazone 30 mg achieved a 26.2% decrease in triglyceride levels from a mean baseline of 214.2 mg/dL compared to an 11.5% decrease for alogliptin alone and a 21.8% decrease for pioglitazone alone. In addition, a 14.4% increase in HDL cholesterol levels from a mean baseline of 43.2 mg/dL was also observed for alogliptin 25 mg with pioglitazone 30 mg compared to a 1.9% increase for alogliptin alone and a 13.2% increase for pioglitazone alone. The changes in measures of LDL cholesterol and total cholesterol were similar between alogliptin 25 mg with pioglitazone 30 mg versus alogliptin alone and pioglitazone alone. A similar pattern of lipid effects was observed in a 26 week, placebo-controlled factorial study.

Alogliptin

Single-dose administration of alogliptin to healthy subjects resulted in a peak inhibition of DPP-4 within two to three hours after dosing. The peak inhibition of DPP-4 exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24 hours to active GLP-1 were three- to four-fold greater with alogliptin (at doses of 25 to 200 mg) than placebo. In a 16 week, double-blind, placebo-controlled study alogliptin 25 mg demonstrated decreases in postprandial glucagon while increasing postprandial active GLP-1 levels compared to placebo over an eight-hour period following a standardized meal. It is unclear how these findings relate to changes in overall glycemic control in patients with type 2 diabetes mellitus. In this study, alogliptin 25 mg demonstrated decreases in two-hour postprandial glucose compared to placebo (-30 mg/dL versus 17 mg/dL respectively).

Multiple-dose administration of alogliptin to patients with type 2 diabetes also resulted in a peak inhibition of DPP-4 within one to two hours and exceeded 93% across all doses (25 mg, 100 mg and 400 mg) after a single dose and after 14 days of once-daily dosing. At these doses of alogliptin, inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing.

Pioglitazone

Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations and lower A1C values. In controlled clinical trials, pioglitazone had an additive effect on glycemic control when used in combination with a sulfonylurea, metformin or insulin [see *Clinical Studies (14)*]. Patients with lipid abnormalities were included in clinical trials with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in serum triglycerides, mean increases in HDL cholesterol and no consistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefit with pioglitazone [see *Warnings and Precautions (5.12)* and *Adverse Reactions (6.1)*].

In a 26 week, placebo-controlled, dose-ranging monotherapy study, mean serum triglycerides decreased in the pioglitazone 15 mg, 30 mg and 45 mg dose groups compared to a mean increase in the placebo group. Mean HDL cholesterol increased to a greater extent in patients treated with pioglitazone than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone compared to placebo (*Table 7*).

Table 7. Lipids in a 26 Week, Placebo-Controlled, Monotherapy, Dose-Ranging Study

	Placebo	Pioglitazone 15 mg Once Daily	Pioglitazone 30 mg Once Daily	Pioglitazone 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	263	284	261	260
Percent change from baseline (adjusted mean*)	4.8%	-9% [†]	-9.6% [†]	-9.3% [†]
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	42	40	41	41
Percent change from baseline (adjusted mean*)	8.1%	14.1% [†]	12.2%	19.1% [†]
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	139	132	136	127
Percent change from baseline (adjusted mean*)	4.8%	7.2%	5.2%	6%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	225	220	223	214
Percent change from baseline (adjusted mean*)	4.4%	4.6%	3.3%	6.4%

*Adjusted for baseline, pooled center and pooled center by treatment interaction

[†]p<0.05 versus placebo

In the two other monotherapy studies (16 weeks and 24 weeks) and in combination therapy studies with sulfonylurea (16 weeks and 24 weeks), metformin (16 weeks and 24 weeks) or insulin (16 weeks and 24 weeks), the lipid results were generally consistent with the data above.

12.3 Pharmacokinetics

Absorption and Bioavailability

Alogliptin and Pioglitazone

In bioequivalence studies of OSENI, the area under the plasma concentration curve (AUC) and maximum concentration (C_{max}) of both the alogliptin and the pioglitazone component following a single dose of the combination tablet (12.5 mg/15 mg or 25 mg/45 mg) were bioequivalent to alogliptin (12.5 mg or 25 mg) concomitantly administered with pioglitazone (15 mg or 45 mg respectively) tablets under fasted conditions in healthy subjects.

Administration of OSENI 25 mg/45 mg with food resulted in no significant change in overall exposure of alogliptin or pioglitazone. OSENI may therefore be administered with or without food.

Alogliptin

The absolute bioavailability of alogliptin is approximately 100%. Administration of alogliptin with a high-fat meal results in no significant change in total and peak exposure to alogliptin. Alogliptin may therefore be administered with or without food.

Pioglitazone

Following oral administration of pioglitazone hydrochloride, peak concentrations of pioglitazone were observed within two hours. Food slightly delays the time to peak serum concentration (T_{max}) to three to four hours but does not alter the extent of absorption (AUC).

Distribution

Alogliptin

Following a single, 12.5 mg intravenous infusion of alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L, indicating that the drug is well distributed into tissues.

Alogliptin is 20% bound to plasma proteins.

Pioglitazone

The mean apparent V_d/F of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean \pm SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Metabolism

Alogliptin

Alogliptin does not undergo extensive metabolism and 60% to 71% of the dose is excreted as unchanged drug in the urine.

Two minor metabolites were detected following administration of an oral dose of [^{14}C] alogliptin, *N*-demethylated, M-I (less than 1% of the parent compound), and *N*-acetylated alogliptin, M-II (less than 6% of the parent compound). M-I is an active metabolite and is an inhibitor of DPP-4 similar to the parent molecule; M-II does not display any inhibitory activity toward DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

Alogliptin exists predominantly as the (*R*)-enantiomer (more than 99%) and undergoes little or no chiral conversion *in vivo* to the (*S*)-enantiomer. The (*S*)-enantiomer is not detectable at the 25 mg dose.

Pioglitazone

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans. Following once-daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within seven days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady-state, in both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20% to 25% of the total AUC.

Maximum serum concentration (C_{max}), AUC and trough serum concentrations (C_{min}) for pioglitazone and M-III and M-IV, increased proportionally with administered doses of 15 mg and 30 mg per day.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms, including the mainly extrahepatic CYP1A1. *In vivo* studies of pioglitazone in combination with gemfibrozil, a strong CYP2C8 inhibitor, showed that pioglitazone is a CYP2C8 substrate [see *Dosage and Administration* (2.3) and *Drug Interactions* (7)]. Urinary 6 β -hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination

Alogliptin

The primary route of elimination of [^{14}C] alogliptin derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr.

Pioglitazone

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Impairment

Alogliptin

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of alogliptin 50 mg in patients with chronic renal impairment compared with healthy subjects.

In patients with mild renal impairment (creatinine clearance [CrCl] \geq 60 to <90 mL/min), an approximate 1.2-fold increase in plasma AUC of alogliptin was observed. Because increases of this magnitude are not considered clinically relevant, dose adjustment for patients with mild renal impairment is not recommended.

In patients with moderate renal impairment (CrCl \geq 30 to <60 mL/min), an approximate two-fold increase in plasma AUC of alogliptin was observed. To maintain similar systemic exposures of OSENI to those with normal renal function, the recommended dose of OSENI is 12.5 mg/15 mg, 12.5 mg/30 mg or 12.5 mg/45 mg once daily in patients with moderate renal impairment.

In patients with severe renal impairment (CrCl \geq 15 to <30 mL/min) and end-stage renal disease (ESRD) (CrCl <15 mL/min or requiring dialysis), an approximate three- and four-fold increase in plasma AUC of alogliptin were observed, respectively. Dialysis removed approximately 7% of the drug during a three-hour dialysis session. OSENI is not recommended for patients with severe renal impairment or ESRD. Coadministration of pioglitazone and alogliptin 6.25 mg once daily based on individual requirements may be considered in these patients.

Pioglitazone

The serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 50 mL/min) to severe (creatinine clearance <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore no dose adjustment in patients with renal impairment is required.

Hepatic Impairment**Alogliptin**

Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment (Child-Pugh Grade B) compared to healthy subjects. The magnitude of these reductions is not considered to be clinically meaningful. Patients with severe hepatic impairment (Child-Pugh Grade C) have not been studied. Use caution when administering OSENI to patients with liver disease [see *Use in Specific Populations (8.7)* and *Warnings and Precautions (5.4)*].

Pioglitazone

Compared with healthy controls, subjects with impaired hepatic function (Child-Pugh Grade B and C) have an approximate 45% reduction in pioglitazone and total pioglitazone (pioglitazone, M-III and M-IV) mean peak concentrations but no change in the mean AUC values. Therefore, no dose adjustment in patients with hepatic impairment is required.

There are postmarketing reports of liver failure with pioglitazone and clinical trials have generally excluded patients with serum ALT >2.5 times the upper limit of the reference range. Use caution in patients with liver disease [see *Warnings and Precautions (5.4)*].

Gender**Alogliptin**

No dose adjustment of alogliptin is necessary based on gender. Gender did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Pioglitazone

The mean C_{max} and AUC values of pioglitazone were increased 20% to 60% in women compared to men. In controlled clinical trials, A1C decreases from baseline were generally greater for females than for males (average mean difference in A1C 0.5%). Because therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Geriatric**Alogliptin**

No dose adjustment of alogliptin is necessary based on age. Age did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Pioglitazone

In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are approximately 21% higher than those achieved in younger subjects. The mean terminal half-life values of pioglitazone were also longer in elderly subjects (about 10 hours) as compared to younger subjects (about seven hours). These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics**Alogliptin**

Studies characterizing the pharmacokinetics of alogliptin in pediatric patients have not been performed.

Pioglitazone

Safety and efficacy of pioglitazone in pediatric patients have not been established. Pioglitazone is not recommended for use in pediatric patients [see *Use in Specific Populations (8.4)*].

Race and Ethnicity**Alogliptin**

No dose adjustment of alogliptin is necessary based on race. Race (White, Black and Asian) did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Pioglitazone

Pharmacokinetic data among various ethnic groups are not available.

Drug Interactions

Coadministration of alogliptin 25 mg once daily with a CYP2C8 substrate, pioglitazone 45 mg once daily for 12 days had no clinically meaningful effects on the pharmacokinetics of pioglitazone and its active metabolites.

Specific pharmacokinetic drug interaction studies with OSENI have not been performed, although such studies have been conducted with the individual components of OSENI (alogliptin and pioglitazone).

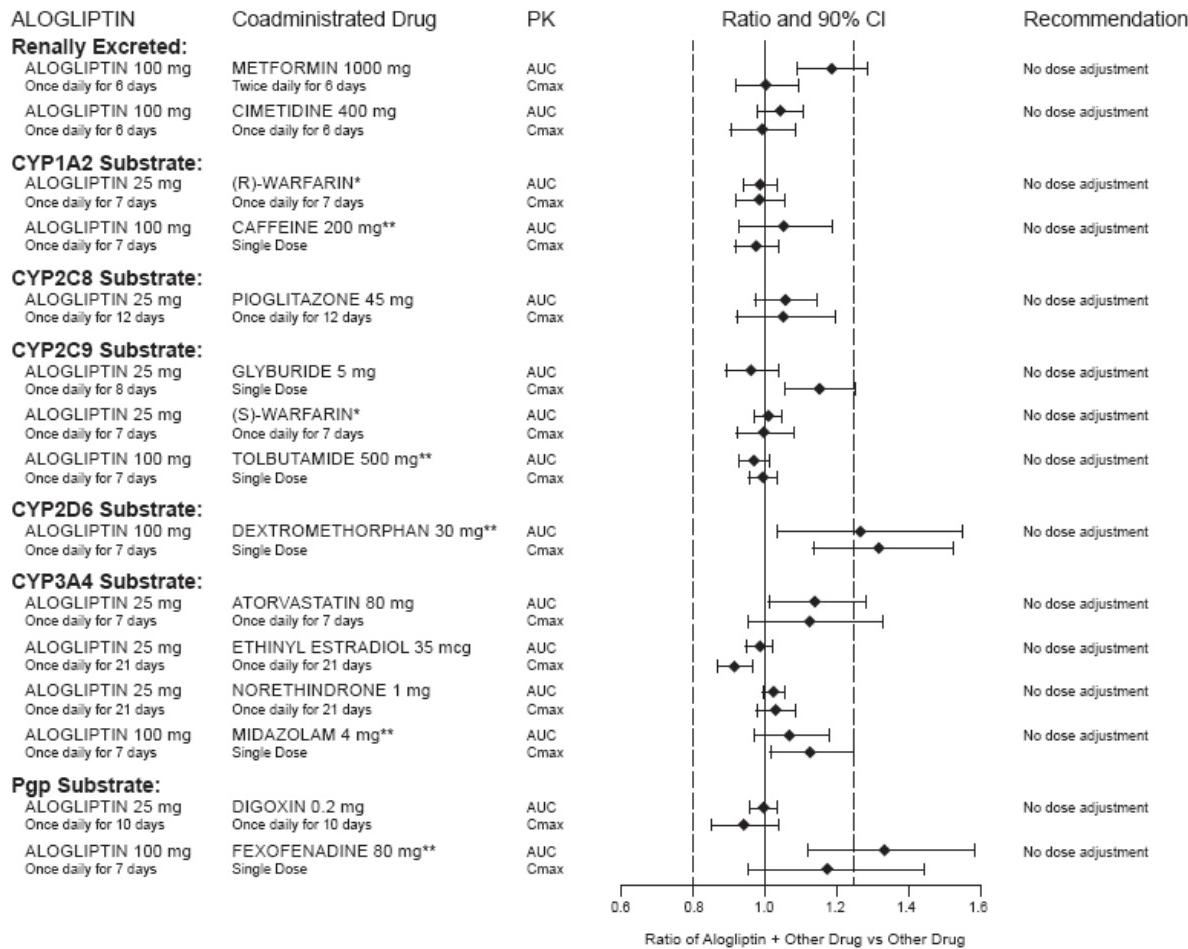
Alogliptin**In Vitro Assessment of Drug Interactions**

In vitro studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions**Effects of Alogliptin on the Pharmacokinetics of Other Drugs**

In clinical studies, alogliptin did not meaningfully increase the systemic exposure to the following drugs that are metabolized by CYP isozymes or excreted unchanged in urine (*Figure 1*). No dose adjustment of alogliptin is recommended based on results of the described pharmacokinetic studies.

Figure 1. Effect of Alogliptin on the Pharmacokinetic Exposure to Other Drugs

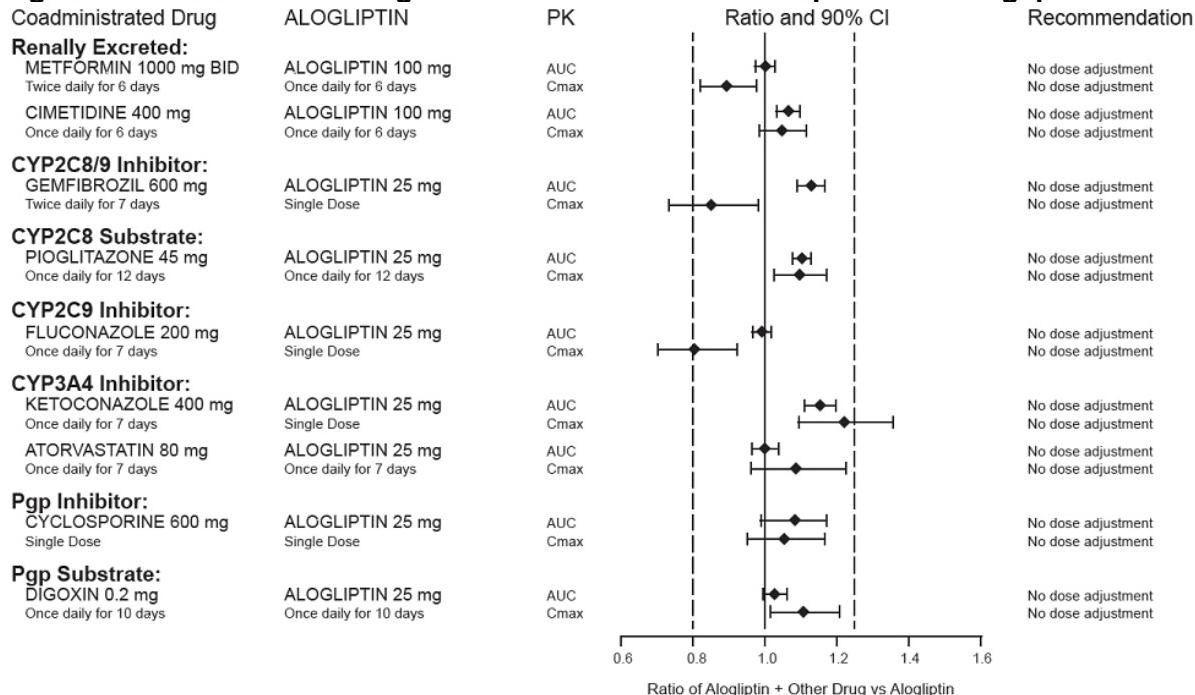


*Warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).

**Caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4 substrate) and fexofenadine (P-gp substrate) were administered as a cocktail.

Effects of Other Drugs on the Pharmacokinetics of Alogliptin

There are no clinically meaningful changes in the pharmacokinetics of alogliptin when alogliptin is administered concomitantly with the drugs described below (Figure 2).

Figure 2. Effect of Other Drugs on the Pharmacokinetic Exposure of Alogliptin

Pioglitazone**Table 8. Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs**

		Coadministered Drug			
Pioglitazone Dosage Regimen (mg)*	Name and Dose Regimens	Change in AUC†		Change in C _{max} †	
45 mg (N=12)	Warfarin‡				
	Daily loading then maintenance doses based PT and INR values Quick's Value=35 ± 5%	R-Warfarin	↓3%	R-Warfarin	↓2%
		S-Warfarin	↓1%	S-Warfarin	↑1%
45 mg (N=12)	Digoxin				
	0.200 mg twice daily (loading dose) then 0.250 mg daily (maintenance dose, 7 days)	↑15%		↑17%	
45 mg daily for 21 days (N=35)	Oral Contraceptive				
	[Ethinyl Estradiol (EE) 0.035 mg plus Norethindrone (NE) 1 mg] for 21 days	EE	↓11%	EE	↓13%
		NE	↑3%	NE	↓7%
45 mg (N=23)	Fexofenadine				
	60 mg twice daily for 7 days	↑30%		↑37%	
45 mg (N=14)	Glipizide				
	5 mg daily for 7 days	↓3%		↓8%	
45 mg daily for 8 days (N=16)	Metformin				
	1000 mg single dose on 8 days	↓3%		↓5%	
45 mg (N=21)	Midazolam				
	7.5 mg single dose on day 15	↓26%		↓26%	
45 mg (N=24)	Ranitidine				
	150 mg twice daily for 7 days	↑1%		↓1%	
45 mg daily for 4 days (N=24)	Nifedipine ER				
	30 mg daily for 4 days	↓13%		↓17%	
45 mg (N=25)	Atorvastatin Ca				
	80 mg daily for 7 days	↓14%		↓23%	
45 mg (N=22)	Theophylline				
	400 mg twice daily for 7 days	↑2%		↑5%	

*Daily for seven days unless otherwise noted

†% change (with/without coadministered drug and no change=0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively

‡Pioglitazone had no clinically significant effect on prothrombin time

Table 9. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure

Coadministered Drug and Dosage Regimen	Pioglitazone		
	Dose Regimen (mg)*	Change in AUC†	Change in C _{max} †
Gemfibrozil 600 mg twice daily for 2 days (N=12)	30 mg single dose	↑3.4-fold‡	↑6%
Ketoconazole 200 mg twice daily for 7 days (N=28)	45 mg	↑34%	↑14%
Rifampin 600 mg daily for 5 days (N=10)	30 mg single dose	↓54%	↓5%
Fexofenadine 60 mg twice daily for 7 days (N=23)	45 mg	↑1%	0%
Ranitidine 150 mg twice daily for 4 days (N=23)	45 mg	↓13%	↓16%
Nifedipine ER 30 mg daily for 7 days (N=23)	45 mg	↑5%	↑4%
Atorvastatin Ca 80 mg daily for 7 days (N=24)	45 mg	↓24%	↓31%
Theophylline 400 mg twice daily for 7 days (N=22)	45 mg	↓4%	↓2%
Topiramate 96 mg twice daily for 7 days§ (N=26)	30 mg §	↓15%¶	0%

*Daily for seven days unless otherwise noted

†Mean ratio (with/without coadministered drug and no change=one-fold) % change (with/without coadministered drug and no change=0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively

‡The half-life of pioglitazone increased from 6.5 hours to 15.1 hours in the presence of gemfibrozil [see *Dosage and Administration (2.3) and Drug Interactions (7)*]

§Indicates duration of concomitant administration with highest twice-daily dose of topiramate from Day 14 onwards over the 22 days of study

¶Additional decrease in active metabolites; 60% for M-III and 16% for M-IV

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Alogliptin and Pioglitazone

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with OSENI. The following data are based on findings in studies performed with alogliptin or pioglitazone individually.

Alogliptin

Rats were administered oral doses of 75, 400 and 800 mg/kg alogliptin for two years. No drug-related tumors were observed up to 75 mg/kg or approximately 32 times the maximum recommended clinical dose of 25 mg, based on area under the plasma concentration curve (AUC) exposure. At higher doses (approximately 308 times the maximum recommended clinical dose of 25 mg), a combination of thyroid C-cell adenomas and carcinomas increased in male but not female rats. No drug-related tumors were observed in mice after administration of 50, 150 or 300 mg/kg alogliptin for two years, or up to approximately 51 times the maximum recommended clinical dose of 25 mg, based on AUC exposure.

Alogliptin was not mutagenic or clastogenic, with and without metabolic activation, in the Ames test with *S. typhimurium* and *E. coli* or the cytogenetic assay in mouse lymphoma cells. Alogliptin was negative in the *in vivo* mouse micronucleus study.

In a fertility study in rats, alogliptin had no adverse effects on early embryonic development, mating or fertility at doses up to 500 mg/kg, or approximately 172 times the clinical dose based on plasma drug exposure (AUC).

Pioglitazone

A two year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the MRHD of 45 mg based on mg/m²). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg and above (approximately equal to the MRHD based on mg/m²). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg (approximately 11 times the MRHD based on mg/m²). No drug-induced tumors were observed in any organ.

Pioglitazone was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone daily prior to and throughout mating and gestation (approximately nine times the MRHD based on mg/m²).

13.2 Animal Toxicology and/or Pharmacology

Pioglitazone

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone (approximately 11, one, and two times the MRHD for mice, rats and dogs, respectively, based on mg/m²). In a one year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg (approximately 35 times the MRHD based on mg/m²). Heart enlargement was seen in a 13 week study in monkeys at oral doses of

8.9 mg/kg and above (approximately four times the MRHD based on mg/m²), but not in a 52 week study at oral doses up to 32 mg/kg (approximately 13 times the MRHD based on mg/m²).

14 CLINICAL STUDIES

The coadministration of alogliptin and pioglitazone has been studied in patients with type 2 diabetes inadequately controlled on either diet and exercise alone or on metformin alone.

There have been no clinical efficacy studies conducted with OSENI; however, bioequivalence of OSENI with coadministered alogliptin and pioglitazone tablets was demonstrated, and efficacy of the combination of alogliptin and pioglitazone has been demonstrated in four Phase 3 efficacy studies.

In patients with type 2 diabetes, treatment with OSENI produced clinically meaningful and statistically significant improvements in A1C compared to either alogliptin or pioglitazone alone. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with OSENI appears to be related to the degree of A1C elevation at baseline.

Alogliptin and Pioglitazone Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

In a 26 week, double-blind, active-controlled study, a total of 655 patients inadequately controlled on diet and exercise alone (mean baseline A1C=8.8%) were randomized to receive alogliptin 25 mg alone, pioglitazone 30 mg alone, alogliptin 12.5 mg with pioglitazone 30 mg or alogliptin 25 mg with pioglitazone 30 mg once daily. Coadministration of alogliptin 25 mg with pioglitazone 30 mg resulted in statistically significant improvements from baseline in A1C and FPG compared to either alogliptin 25 mg alone or to pioglitazone 30 mg alone (*Table 10*). Coadministration of alogliptin 25 mg with pioglitazone 30 mg once daily resulted in statistically significant reductions in fasting plasma glucose (FPG) starting from Week 2 through Week 26 compared to either alogliptin 25 mg or pioglitazone 30 mg alone. A total of 3% of patients receiving alogliptin 25 mg coadministered with pioglitazone 30 mg, 11% of those receiving alogliptin 25 mg alone, and 6% of those receiving pioglitazone 30 mg alone required glycemic rescue.

Improvements in A1C were not affected by gender, age or baseline BMI.

The mean increase in body weight was similar between pioglitazone alone and alogliptin when coadministered with pioglitazone.

Table 10. Glycemic Parameters at Week 26 in a Coadministration Study of Alogliptin and Pioglitazone in Patients Inadequately Controlled on Diet and Exercise*

	Alogliptin 25 mg	Pioglitazone 30 mg	Alogliptin 25 mg + Pioglitazone 30 mg
A1C (%)	N=160	N=153	N=158
Baseline (mean)	8.8	8.8	8.8
Change from Baseline (adjusted mean [†])	-1	-1.2	-1.7
Difference from alogliptin 25 mg (adjusted mean [†] with 95% confidence interval)			-0.8 [‡] (-1, -0.5)
Difference from pioglitazone 30 mg (adjusted mean [†] with 95% confidence interval)			-0.6 [‡] (-0.8, -0.3)
% of Patients (n/N) achieving A1C ≤ 7%	24% (40/164)	34% (55/163)	63% (103/164) [‡]
FPG (mg/dL)	N=162	N=157	N=162
Baseline (mean)	189	189	185
Change from Baseline (adjusted mean [†])	-26	-37	-50
Difference from alogliptin 25 mg (adjusted mean [†] with 95% confidence interval)			-25 [‡] (-34, -15)
Difference from pioglitazone 30 mg (adjusted mean [†] with 95% confidence interval)			-13 [‡] (-22, -4)

*Intent-to-treat population using last observation carried forward

[†]Least squares means adjusted for treatment, geographic region and baseline value[‡]p<0.01 compared to alogliptin 25 mg or pioglitazone 30 mg

Alogliptin and Pioglitazone Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

In the second 26 week, double-blind, placebo-controlled study, a total of 1554 patients already on metformin (mean baseline A1C=8.5%) were randomized to one of 12 double-blind treatment groups: placebo; 12.5 mg or 25 mg of alogliptin alone; 15 mg, 30 mg or 45 mg of pioglitazone alone; or 12.5 mg or 25 mg of alogliptin in combination with 15 mg, 30 mg or 45 mg of pioglitazone. Patients were maintained on a stable dose of metformin (median dose=1700 mg) during the treatment period. Coadministration of alogliptin and pioglitazone provided statistically significant improvements in A1C and FPG compared to placebo, to alogliptin alone, or to pioglitazone alone when added to background metformin therapy (*Table 11, Figure 3*). A total of 4%, 5% or 2% of patients receiving alogliptin 25 mg with 15 mg, 30 mg or 45 mg pioglitazone, 33% of patients receiving placebo, 13% of patients receiving alogliptin 25 mg, and 10%, 15% or 9% of patients receiving pioglitazone 15 mg, 30 mg or 45 mg alone required glycemic rescue.

Improvements in A1C were not affected by gender, age or baseline BMI.

The mean increase in body weight was similar between pioglitazone alone and alogliptin when coadministered with pioglitazone.

Table 11. Glycemic Parameters at Week 26 for Alogliptin and Pioglitazone Alone and in Combination in Patients with Type 2 Diabetes*

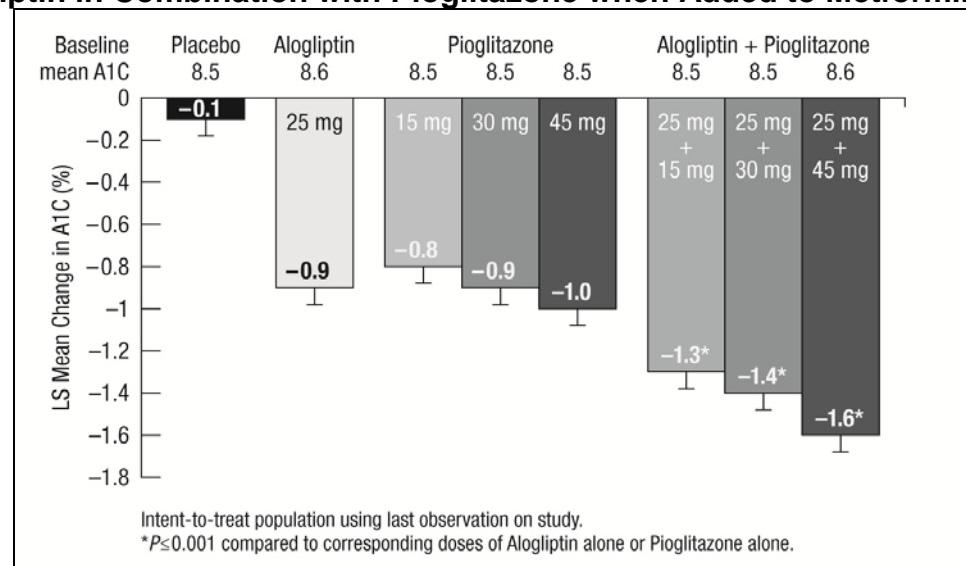
	Placebo	Alogliptin 25 mg	Pioglitazone 15 mg	Pioglitazone 30 mg	Pioglitazone 45 mg	Alogliptin 25 mg + Pioglitazone 15 mg	Alogliptin 25 mg + Pioglitazone 30 mg	Alogliptin 25 mg + Pioglitazone 45 mg
A1C (%)	N=126	N=123	N=127	N=123	N=126	N=127	N=124	N=126
Baseline (mean)	8.5	8.6	8.5	8.5	8.5	8.5	8.5	8.6
Change from baseline (adjusted mean [†] with 95% confidence interval)	-0.1	-0.9	-0.8	-0.9	-1	-1.3 [‡]	-1.4 [‡]	-1.6 [‡]
Difference from pioglitazone (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-0.5 [‡] (-0.7, -0.3)	-0.5 [‡] (-0.7, -0.3)	-0.6 [‡] (-0.8, -0.4)
Difference from alogliptin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-0.4 [‡] (-0.6, -0.1)	-0.5 [‡] (-0.7, -0.3)	-0.7 [‡] (-0.9, -0.5)
Patients (%) achieving A1C ≤7%	6% (8/129)	27% (35/129)	26% (33/129)	30% (38/129)	36% (47/129)	55% (71/130) [‡]	53% (69/130) [‡]	60% (78/130) [‡]
FPG (mg/dL)	N=129	N=126	N=127	N=125	N=129	N=130	N=126	N=127
Baseline (mean)	177	184	177	175	181	179	179	178
Change from baseline (adjusted mean [†] with 95% confidence interval)	7	-19	-24	-29	-32	-38 [‡]	-42 [‡]	-53 [‡]
Difference from pioglitazone (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-14 [‡] (-24, -5)	-13 [‡] (-23, -3)	-20 [‡] (-30, -11)
Difference from alogliptin (adjusted mean [†] with 95% confidence interval)	-	-	-	-	-	-19 [‡] (-29, -10)	-23 [‡] (-33, -13)	-34 [‡] (-44, -24)

*Intent-to-treat population using last observation carried forward

†Least squares means adjusted for treatment, geographic region metformin dose and baseline value

‡p≤0.01 when compared to pioglitazone and alogliptin alone

Figure 3. Change from Baseline in A1C at Week 26 with Alogliptin and Pioglitazone Alone and Alogliptin in Combination with Pioglitazone when Added to Metformin



Alogliptin Add-On Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin in Combination with Pioglitazone

In a 52 week, active-comparator study, a total of 803 patients inadequately controlled (mean baseline A1C=8.2%) on a current regimen of pioglitazone 30 mg and metformin at least 1500 mg per day or at the maximum tolerated dose were randomized to either receive the addition of alogliptin 25 mg or the titration of pioglitazone 30 mg to 45 mg following a four week, single-blind, placebo run-in period. Patients were maintained on a stable dose of metformin (median dose=1700 mg). Patients who failed to meet prespecified hyperglycemic goals during the 52 week treatment period received glycemic rescue therapy.

In combination with pioglitazone and metformin, alogliptin 25 mg was shown to be statistically superior in lowering A1C and FPG compared with the titration of pioglitazone from 30 mg to 45 mg at Week 26 and Week 52 (*Table 12, results shown only for Week 52*). A total of 11% of patients who were receiving alogliptin 25 mg in combination with pioglitazone 30 mg and metformin and 22% of patients receiving a dose titration of pioglitazone from 30 mg to 45 mg in combination with metformin required glycemic rescue.

Improvements in A1C were not affected by gender, age, race or baseline BMI. The mean increase in body weight was similar in both treatment arms. Lipid effects were neutral.

Table 12. Glycemic Parameters at Week 52 in an Active-Controlled Study of Alogliptin as Add-On Combination Therapy to Metformin and Pioglitazone*

	Alogliptin 25 mg + Pioglitazone 30 mg + Metformin	Pioglitazone 45 mg + Metformin
A1C (%)	N=397	N=394
Baseline (mean)	8.2	8.1
Change from Baseline (adjusted mean [†])	-0.7	-0.3
Difference from Pioglitazone 45 mg + Metformin (adjusted mean [†] with 95% confidence interval)	-0.4 [‡] (-0.5, -0.3)	-
% of Patients (n/N) achieving A1C ≤7%	33% (134/404) [§]	21% (85/399)
FPG (mg/dL)	N=399	N=396
Baseline (mean)	162	162
Change from Baseline (adjusted mean [†])	-15	-4
Difference from Pioglitazone 45 mg + Metformin (adjusted mean [†] with 95% confidence interval)	-11 [§] (-16, -6)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose[‡]Noninferior and statistically superior to metformin plus pioglitazone at the 0.025 one-sided significance level[§]p<0.001 compared to pioglitazone 45 mg + metformin

Alogliptin Add-On Therapy to a Thiazolidinedione

A 26 week, placebo-controlled study, was conducted to evaluate the efficacy and safety of alogliptin as add-on therapy to pioglitazone in patients with type 2 diabetes. A total of 493 patients inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea (mean baseline A1C=8%) were randomized to receive alogliptin 12.5 mg, alogliptin 25 mg or placebo.

Patients were maintained on a stable dose of pioglitazone (median dose=30 mg) during the treatment period and those who were also previously treated on metformin (median dose=2000 mg) or sulfonylurea (median dose=10 mg) prior to randomization were maintained on the combination therapy during the treatment period. All patients entered into a four week, single-blind, placebo run-in period prior to randomization. Following randomization, all patients continued to receive instruction on diet and exercise. Patients who failed to meet prespecified hyperglycemic goals during the 26 week treatment period received glycemic rescue.

The addition of alogliptin 25 mg once daily to pioglitazone therapy resulted in significant improvements from baseline in A1C and FPG at Week 26 when compared to the addition of placebo (*Table 13*). A total of 9% of patients who were receiving alogliptin 25 mg and 12% of patients receiving placebo required glycemic rescue.

The improvement in A1C was not affected by gender, age, baseline BMI or baseline pioglitazone dose. The mean increase in body weight was similar between alogliptin and placebo when given in combination with pioglitazone. Lipid effects were neutral.

Table 13. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of Alogliptin as Add-On Therapy to Pioglitazone*

	Alogliptin 25 mg + Pioglitazone ± Metformin ± Sulfonylurea	Placebo + Pioglitazone ± Metformin ± Sulfonylurea
A1C (%)	N=195	N=95
Baseline (mean)	8	8
Change from baseline (adjusted mean [†])	-0.8	-0.2
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-0.6 [‡] (-0.8, -0.4)	-
% of patients (n/N) achieving A1C ≤7%	49% (98/199) [‡]	34% (33/97)
FPG (mg/dL)	N=197	N=97
Baseline (mean)	170	172
Change from baseline (adjusted mean [†])	-20	-6
Difference from placebo (adjusted mean [†] with 95% confidence interval)	-14 [‡] (-23, -5)	-

*Intent-to-treat population using last observation on study

[†]Least squares means adjusted for treatment, baseline value, geographic region, baseline treatment regimen (pioglitazone, pioglitazone + metformin or pioglitazone + sulfonylurea) and baseline pioglitazone dose

[‡]p<0.01 compared to placebo

Cardiovascular Safety Trial

A randomized, double-blind, placebo-controlled cardiovascular outcomes trial (EXAMINE) was conducted to evaluate the cardiovascular risk of alogliptin. The trial compared the risk of major adverse cardiovascular events (MACE) between alogliptin (N=2701) and placebo (N=2679) when added to standard of care therapies for diabetes and atherosclerotic vascular disease (ASCVD). The trial was event driven and patients were followed until a sufficient number of primary outcome events accrued.

Eligible patients were adults with type 2 diabetes who had inadequate glycemic control at baseline (e.g., HbA1c >6.5%) and had been hospitalized for an acute coronary syndrome event (e.g., acute

myocardial infarction or unstable angina requiring hospitalization) 15 to 90 days prior to randomization. The dose of alogliptin was based on estimated renal function at baseline per dosage and administration recommendations [see *Dosage and Administration (2.2)*]. The average time between an acute coronary syndrome event and randomization was approximately 48 days.

The mean age of the population was 61 years. Most patients were male (68%), Caucasian (73%), and were recruited from outside of the United States (86%). Asian and Black patients contributed 20% and 4% of the total population, respectively. At the time of randomization patients had a diagnosis of type 2 diabetes mellitus for approximately 9 years, 87% had a prior myocardial infarction and 14% were current smokers. Hypertension (83%) and renal impairment (27% with an eGFR ≤60 ml/min/1.73 m²) were prevalent co-morbid conditions. Use of medications to treat diabetes (e.g., metformin 73%, sulfonylurea 54%, insulin 41%), and ASCVD (e.g., statin 94%, aspirin 93%, renin-angiotensin system blocker 88%, beta-blocker 87%) was similar between patients randomized to alogliptin and placebo at baseline. During the trial, medications to treat diabetes and ASCVD could be adjusted to ensure care for these conditions adhered to standard of care recommendations set by local practice guidelines.

The primary endpoint in EXAMINE was the time to first occurrence of a MACE defined as the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. The study was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE. The median exposure to study drug was 526 days and 95% of the patients were followed to study completion or death.

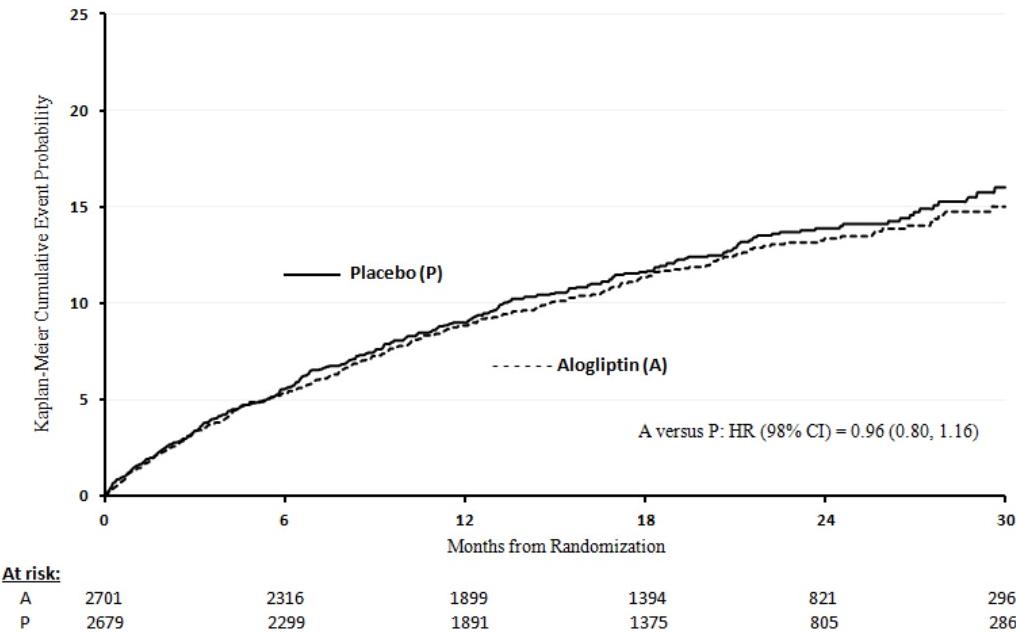
Table 14 shows the study results for the primary MACE composite endpoint and the contribution of each component to the primary MACE endpoint. The upper bound of the confidence interval was 1.16 and excluded a risk margin larger than 1.3.

Table 14. Patients with MACE in EXAMINE

Composite of first event of CV death, nonfatal MI or nonfatal stroke (MACE)	Alogliptin		Placebo		Hazard Ratio
	Number of Patients (%)	Rate per 100 PY*	Number of Patients (%)	Rate per 100 PY*	(98% CI)
	N=2701		N=2679		
	305 (11.3)	7.6	316 (11.8)	7.9	0.96 (0.80, 1.16)
CV Death	89 (3.3)	2.2	111 (4.1)	2.8	
Nonfatal MI	187 (6.9)	4.6	173 (6.5)	4.3	
Nonfatal stroke	29 (1.1)	0.7	32 (1.2)	0.8	

*Patient Years (PY)

The Kaplan-Meier based cumulative event probability is presented in Figure 4 for the time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for placebo and alogliptin overlap throughout the duration of the study. The observed incidence of MACE was highest within the first 60 days after randomization in both treatment arms (14.8 MACE per 100 PY), decreased from day 60 to the end of the first year (8.4 per 100 PY) and was lowest after one year of follow-up (5.2 per 100 PY).

Figure 4. Observed Cumulative Rate of MACE in EXAMINE

The rate of all cause death was similar between treatment arms with 153 (3.6 per 100 PY) recorded among patients randomized to alogliptin and 173 (4.1 per 100 PY) among patients randomized to placebo. A total of 112 deaths (2.9 per 100 PY) among patients on alogliptin and 130 among patients on placebo (3.5 per 100 PY) were adjudicated as cardiovascular deaths.

16 HOW SUPPLIED/STORAGE AND HANDLING

OSENI tablets are available in the following strengths and packages:

25 mg/15 mg tablet: yellow, round, biconvex and film-coated with both “A/P” and “25/15” printed on one side, available in:

NDC 64764-251-03	Bottles of 30 tablets
NDC 64764-251-04	Bottles of 90 tablets
NDC 64764-251-05	Bottles of 500 tablets

25 mg/30 mg tablet: peach, round, biconvex and film-coated with both “A/P” and “25/30” printed on one side, available in:

NDC 64764-253-03	Bottles of 30 tablets
NDC 64764-253-04	Bottles of 90 tablets
NDC 64764-253-05	Bottles of 500 tablets

25 mg/45 mg tablet: red, round, biconvex, film-coated and with both “A/P” and “25/45” printed on one side, available in:

NDC 64764-254-03	Bottles of 30 tablets
NDC 64764-254-04	Bottles of 90 tablets
NDC 64764-254-05	Bottles of 500 tablets

12.5 mg/15 mg tablet: pale yellow, round, biconvex and film-coated with both "A/P" and "12.5/15" printed on one side, available in:

NDC 64764-121-03	Bottles of 30 tablets
NDC 64764-121-04	Bottles of 90 tablets
NDC 64764-121-05	Bottles of 500 tablets

12.5 mg/30 mg tablet: pale peach, round, biconvex and film-coated with both "A/P" and "12.5/30" printed on one side, available in:

NDC 64764-123-03	Bottles of 30 tablets
NDC 64764-123-04	Bottles of 90 tablets
NDC 64764-123-05	Bottles of 500 tablets

12.5 mg/45 mg tablet: pale red, round, biconvex and film-coated with both "A/P" and "12.5/45" printed on one side, available in:

NDC 64764-124-03	Bottles of 30 tablets
NDC 64764-124-04	Bottles of 90 tablets
NDC 64764-124-05	Bottles of 500 tablets

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed and protect from moisture and humidity.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the potential risks and benefits of OSENI.

Patients should be informed of the signs and symptoms of heart failure. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on OSENI should immediately report these symptoms to their physician. Before initiating OSENI, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment.

Patients should be informed that acute pancreatitis has been reported during use of alogliptin. Patients should be informed that persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue OSENI and contact their physician if persistent severe abdominal pain occurs.

Patients should be informed that allergic reactions have been reported during use of alogliptin and pioglitazone. If symptoms of allergic reactions (including skin rash, hives and swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing) occur, patients should be instructed to discontinue OSENI and seek medical advice promptly.

Patients should be informed that postmarketing reports of liver injury, sometimes fatal, have been reported during use of alogliptin and pioglitazone. If signs or symptoms of liver injury occur (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia or dark urine), patients should be instructed to discontinue OSENI and seek medical advice promptly.

Tell patients to promptly report any sign of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment, as these may be due to bladder cancer.

Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue or insulin is used in combination with OSENI. Explain the risks, symptoms and appropriate management of hypoglycemia.

Inform female patients that treatment with pioglitazone, like other thiazolidinediones, may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation [see *Use in Specific Populations (8.3)*].

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [see *Warnings and Precautions (5.11)*].

Instruct patients to take OSENI only as prescribed daily. OSENI can be taken with or without meals. If a dose is missed, advise patients not to double their next dose.

Patients should be informed that the tablets must never be split.

Instruct patients to read the Medication Guide before starting OSENI therapy and to reread each time the prescription is refilled. Instruct patients to inform their healthcare provider if an unusual symptom develops or if a symptom persists or worsens.

ALP008 R9

MEDICATION GUIDE

OSENI (OH-senn-ee) (alogliptin and pioglitazone) tablets

Read this Medication Guide carefully before you start taking OSENI and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about OSENI, ask your doctor or pharmacist.

What is the most important information I should know about OSENI?

OSENI can cause serious side effects, including:

1. **Heart failure:** OSENI can cause heart failure and cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure.

Before you start taking OSENI:

Tell your doctor if you have ever had heart failure or have problems with your kidneys.

Call your doctor right away if you have any of the following symptoms:

- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- swelling or fluid retention, especially in the feet, ankles, or legs

These may be symptoms of heart failure.

2. **Inflammation of the pancreas (pancreatitis):** Alogliptin, one of the medicines in OSENI, may cause pancreatitis, which may be severe. Certain medical conditions make you more likely to get pancreatitis.

Before you start taking OSENI:

Tell your doctor if you have ever had:

- pancreatitis
- kidney problems
- liver problems

Stop taking OSENI and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is OSENI?

- OSENI contains 2 prescription diabetes medicines, alogliptin (NESINA) and pioglitazone (ACTOS).
- OSENI is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- OSENI is not for people with type 1 diabetes.
- OSENI is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if OSENI is safe and effective in children under the age of 18. OSENI is not recommended for use in children.

Who should not take OSENI?

Do not take OSENI if you:

- have severe heart failure
- are allergic to alogliptin (NESINA), pioglitazone (ACTOS) or any ingredient in OSENI or have had a serious allergic (hypersensitivity) reaction to alogliptin or pioglitazone. See the end of this Medication Guide for a complete list of the ingredients in OSENI.

Symptoms of a serious allergic reaction to OSENI may include:

- | | |
|--|---|
| <ul style="list-style-type: none"> ◦ swelling of your face, lips, throat and other areas on your skin ◦ raised, red areas on your skin (hives) | <ul style="list-style-type: none"> ◦ difficulty with swallowing or breathing ◦ skin rash, itching, flaking or peeling |
|--|---|

If you have these symptoms, stop taking OSENI and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before and during treatment with OSENI?

Before you start taking OSENI, tell your doctor if you:

- have heart failure

- have a type of diabetic eye disease that causes swelling of the back of the eye (macular edema)
- have kidney or liver problems
- have or have had inflammation of the pancreas (pancreatitis)
- have or have had cancer of the bladder
- have other medical conditions
- **are pregnant or plan to become pregnant.** It is not known if OSENI can harm your unborn baby. Talk to your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant.
- **are a premenopausal woman who does not have periods regularly or at all.** OSENI may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking OSENI. Tell your doctor right away if you become pregnant while taking OSENI.
- **are breastfeeding or plan to breastfeed.** It is not known whether OSENI passes into your breast milk and if it can harm your baby. Talk with your doctor about the best way to control your blood glucose levels while breastfeeding.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist before you start a new medicine.

OSENI may affect the way other medicines work, and other medicines may affect how OSENI works. Contact your doctor before you start or stop other types of medicines.

How should I take OSENI?

- Take OSENI exactly as your doctor tells you to take it.
- Take OSENI 1 time each day with or without food.
- Do not break or cut OSENI tablets before swallowing.
- Your doctor may need to change your dose of OSENI to control your blood glucose. Do not change your dose unless told to do so by your doctor.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and take the next dose at your regular time. **Do not** take 2 doses of OSENI at the same time.
- If you take too much OSENI, call your doctor or go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start OSENI and during treatment as needed. Your doctor may change your dose of OSENI based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor should check your eyes regularly while you take OSENI.

What are the possible side effects of OSENI?

OSENI can cause serious side effects, including:

- See “**What is the most important information I should know about OSENI?**”
- **Allergic (hypersensitivity) reactions**, such as:

- | | |
|--|--|
| <ul style="list-style-type: none"> ○ swelling of your face, lips, throat and other areas on your skin ○ raised, red areas on your skin (hives) | <ul style="list-style-type: none"> ○ difficulty swallowing or breathing ○ skin rash, itching, flaking or peeling |
|--|--|

If you have these symptoms, stop taking OSENI and contact your doctor right away.

- **Liver problems.** Call your doctor right away if you have unexplained symptoms such as:

- | | | |
|--|--|---|
| <ul style="list-style-type: none"> ○ nausea or vomiting ○ loss of appetite | <ul style="list-style-type: none"> ○ stomach pain ○ dark urine | <ul style="list-style-type: none"> ○ unusual or unexplained tiredness ○ yellowing of your skin or the whites of your eyes |
|--|--|---|

- **Broken bones (fractures).** Usually in the hand, upper arm or foot in women. Talk to your doctor for advice on how to keep your bones healthy.

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take OSENI. You should not take OSENI if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
 - blood or a red color in your urine
 - an increased need to urinate
 - pain while you urinate
- **Low blood sugar (hypoglycemia).** If you take OSENI with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take OSENI. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your doctor. Signs and symptoms of low blood sugar may include:
 - shaking or feeling jittery
 - sweating
 - fast heartbeat
 - change in vision
 - hunger
 - headache
 - change in mood
 - confusion
 - dizziness
- **Diabetic eye disease with swelling in the back of the eye (macular edema).** Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly.
- **Release of an egg from an ovary in a woman (ovulation) leading to pregnancy.** Ovulation may happen when premenopausal women who do not have regular monthly periods take OSENI. This can increase your chance of getting pregnant.
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in OSENI, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in OSENI, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking OSENI.

The most common side effects of OSENI include stuffy or runny nose and sore throat, back pain, cold-like symptoms (upper respiratory tract infection).

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OSENI. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OSENI?

- Store OSENI at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep container tightly closed and protect from moisture and humidity.

Keep OSENI and all medicines out of the reach of children.

General information about the safe and effective use of OSENI

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take OSENI for a condition for which it was not prescribed. Do not give OSENI to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about OSENI. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about OSENI that is written for health professionals.

For more information, go to www.oseni.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in OSENI?

Active ingredients: alogliptin and pioglitazone.

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, and lactose monohydrate; the tablets are film-coated with hypromellose, polyethylene glycol, titanium dioxide, talc and ferric oxide (yellow and/or red) and are marked with red A1 or gray F1 printing ink.

Distributed by **Takeda Pharmaceuticals America, Inc.** Deerfield, IL 60015. OSENI, NESINA and ACTOS are trademarks of Takeda Pharmaceutical Company Limited registered with the U.S. Patent and Trademark Office and are used under license by Takeda Pharmaceuticals America, Inc.

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ALP008 R9

This Medication Guide has been approved by the U.S. Food and Drug Administration.

12/2016

EXHIBIT 8



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271

NDA APPROVAL

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) dated and received December 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nesina (alogliptin) tablets, 6.25 mg, 12.5 mg, and 25 mg.

We acknowledge receipt of your amendments dated February 20 and 22, March 21, April 1 and 24, May 7, 9, 16, and 30, June 26, July 22 and 31, August 5, 11, 25, and 29, September 5, October 3, 16, 17, and 29, November 10, 13, and 18, and December 17 and 18, 2008, and January 19 and 21, March 4, 10, 16, and 25, April 9, May 6, 20, and 28, August 31, and October 28, 2009, and January 21, February 11, March 15, April 13, May 7, June 21, and July 21, 2010, and May 25, July 13 and 25, August 25, September 14, October 5, 6, and 11, November 7, 17, and 22, and December 2, 7, and 20, 2011, and January 20 (2), 23, and 24 (2), February 1, 9, 13, 14, and 22 (2), March 6, 8, 13, 22, 23, 26, 27, 28, and 30, April 4, 5, 19, 27, and 30, May 30, July 12 and 26, August 1 (2), 2, 6, 14, and 27, September 13 and 25, October 5, 10, 11, and 23, November 1, 7, 9, 15, 16, 27, and 30, and December 18, 2012, and January 7 (2), 9 (2), 11, and 17, 2013. We also acknowledge receipt of your emails dated January 24 and 25, 2013 that included the agreed-upon labeling.

The submission dated July 26, 2012, constituted a complete response to our action letter dated April 25, 2012.

This new drug application provides for the use of Nesina (alogliptin) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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Page 2

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels submitted on **January 17, 2013**, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022271**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRY DATING PERIOD

A 30-month expiry dating period is granted for Nesina (alogliptin) 6.25 mg tablets and a 36-month expiry dating period is granted for Nesina 12.5 mg and 25 mg tablets when stored at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

ADVISORY COMMITTEE

Your application for Nesina was not referred to an FDA advisory committee because this drug is not the first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 9 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

2007-1: A clinical pharmacology study in pediatric patients with type 2 diabetes to evaluate the pharmacokinetics of alogliptin and to determine the dose(s) for the subsequent Phase 3 studies that will be conducted under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive). At least 25% of randomized subjects will be 10-13 years of age.

Study Completion: December 31, 2013
Final Report Submission: June 30, 2014

2007-2: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Final Protocol Submission: July 31, 2015
Study Completion: July 31, 2019
Final Report Submission: January 31, 2020

NDA 022271
Page 4

2007-3: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Final Protocol Submission: July 31, 2015
Study Completion: November 30, 2020
Final Report Submission: May 31, 2021

Submit the protocols to your IND 069707, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of hepatotoxicity, acute pancreatitis, hypersensitivity reactions, cardiovascular events, serious hypoglycemia, and renal impairment in patients treated with Nesina (alogliptin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2007-4: An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) in patients treated with Nesina (alogliptin). Specialized follow-up should be obtained on these cases to collect additional information on the events. This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and

NDA 022271
Page 5

10 years from the date of approval for reports of serious hepatic abnormalities and severe hypersensitivity reactions.

The timetable you submitted on January 21, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 31, 2013
Interim Report Submissions:	March 31, 2014
	March 31, 2015
	March 31, 2016
	March 31, 2017
	March 31, 2018
	March 31, 2019
	March 31, 2020
	March 31, 2021
	March 31, 2022
Study Completion:	January 31, 2023
Final Report Submission:	September 30, 2023

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with Nesina (alogliptin). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with antidiabetic medications, including Nesina (alogliptin). Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2007-5: A randomized, double-blind, placebo-controlled trial evaluating the effect of Nesina (alogliptin) on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. The primary objective of the trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Nesina (alogliptin) to that observed in the control group is less than 1.3. The long-term effects of Nesina (alogliptin) on hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycemia, pancreatitis, and renal safety will also be evaluated. The trial must include at least 200 Nesina (alogliptin)-treated patients with moderate renal impairment and 100 Nesina (alogliptin)-treated patients with severe renal impairment

The timetable you submitted on January 21, 2013, states that you will conduct this trial according to the following schedule:

Trial Completion:	December 31, 2013
Final Report Submission:	September 30, 2014

NDA 022271
Page 6

Submit the protocol to your IND 069707, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”.**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

(See appended electronic signature page)

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Prescribing Information
Medication Guide
Carton and Container Labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH

01/25/2013

I am approving the single-entity alogliptin first, before approving the combination products containing alogliptin.

EXHIBIT 9



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203414

NDA APPROVAL

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) dated and received November 22, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kazano (alogliptin and metformin hydrochloride) tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg.

We acknowledge receipt of your amendments dated November 28, 2011, and January 16, 18, 20 (2), 23, and 24, February 1 (2), 10, 14, and 22 (2), March 8, 20, 22, 23, and 27, April 2, 3, 4, 5, 19, and 23, May 1, 7, 16, 24, 25, and 29, June 4, 7, 12 (2), 13, 19, and 27, July 9, 10, and 19, August 2, 6, 7, 14, 16 (2), and 27, September 13 and 25, October 5, 10, and 11, November 1, 7, 9, 15, 27, and 30, and December 6, 17, and 18, 2012, and January 7 (2), 9 (2), 11, and 17, 2013. We also acknowledge receipt of your emails dated January 24 and 25, 2013 that included the agreed-upon labeling.

This new drug application provides for the use of Kazano (alogliptin and metformin hydrochloride fixed-dose combination) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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Page 2

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package and text for the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels submitted on **January 17, 2013**, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203414**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRY DATING PERIOD

A 36-month expiry dating period is granted for Kazano (alogliptin and metformin hydrochloride) tablets when stored at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

ADVISORY COMMITTEE

Your application for Kazano was not referred to an FDA advisory committee because this drug is not the first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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Page 3

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 9 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2009-1: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Final Protocol Submission: July 31, 2015
Study Completion: July 31, 2019
Final Report Submission: January 31, 2020

Submit the protocol to your IND 101628, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of hepatotoxicity, acute pancreatitis, and hypersensitivity reactions in patients treated with Kazano (alogliptin and metformin hydrochloride).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2009-2: An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) in patients treated with Kazano (alogliptin and metformin hydrochloride). Specialized follow-up should be obtained on these cases to collect additional information on the events. This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and 10 years from the date of approval for reports of serious hepatic abnormalities and severe hypersensitivity reactions.

The timetable you submitted on January 21, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 31, 2013
Interim Report Submissions:	March 31, 2014
	March 31, 2015
	March 31, 2016
	March 31, 2017
	March 31, 2018
	March 31, 2019
	March 31, 2020
	March 31, 2021
	March 31, 2022
Study Completion:	January 31, 2023
Final Report Submission:	September 30, 2023

Submit the protocol to your IND 101628, with a cross-reference letter to this NDA. Submit all interim and final reports to your NDA. Prominently identify the submission with the following

NDA 203414
Page 5

wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”.**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Prescribing Information
Medication Guide
Carton and Container Labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH

01/25/2013

EXHIBIT 10



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022426

NDA APPROVAL

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) dated September 19, 2008, received September 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oseni (alogliptin and pioglitazone) tablets, 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg.

We also refer to our approval letter dated January 25, 2013, which contained the following error: page 88 of 102 incorrectly displays an earlier draft version of the blister wallet package for the 25 mg/30 mg strength, 7-count labeling. This draft version contained the statement "Package Not Child Resistant". A design change was made to this component making it child resistant and the statement was removed from the packaging in the final draft.

This replacement approval letter incorporates the correct version of the blister wallet package label. The effective approval date will remain January 25, 2013, the date of the original approval letter.

We acknowledge receipt of your amendments dated October 6 and 29, and November 13 and 14, 2008, and January 9, 19, and 28, March 30, April 14, May 6, 20, 22, 26, and 29, June 16, 18, and 30, and October 28, 2009, and January 21, February 11, March 15, April 13, May 7, June 21, and July 21, 2010, and April 19, May 25 and 31, July 13, 25, and 27, August 25, September 9 and 14, October 18 (2) and 28, November 7 and 17, and December 2, 7, 13, and 20, 2011, and January 20, 23, and 24, February 1, 9, 13, 14, and 22 (2), March 6, 8, 13, 22, 23, 26, 27, 28, and 30, April 4, 5, 12, 19, 27, and 30, May 30, July 12 and 27, August 1 (2), 2, 6, 8, and 14, September 13 and 25, October 5 and 10, November 1, 9, 15, 16, 27, and 30, and December 18, 2012, and January 7 (2), 9, 11, and 17, 2013. We also acknowledge receipt of your emails dated January 24 and 25, 2013 that included the agreed-upon labeling.

The submission dated July 27, 2012, constituted a complete response to our action letter dated April 25, 2012.

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Page 2

This new drug application provides for the use of Oseni (alogliptin and pioglitazone fixed-dose combination) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package and text for the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels submitted on **January 17, 2013**, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022426.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRY DATING PERIOD

A 24-month expiry dating period is granted for Oseni (alogliptin and pioglitazone) tablets of all strengths when stored at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

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ADVISORY COMMITTEE

Your application for Oseni was not referred to an FDA advisory committee because this drug is not the first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of hepatotoxicity, acute pancreatitis, and hypersensitivity reactions in patients treated with Oseni (alogliptin and pioglitazone).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2008-1:** An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) in patients treated with Oseni (alogliptin and pioglitazone). Specialized follow-up should be obtained on these cases to collect additional information on the events. This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and 10 years from the date of approval for reports of serious hepatic abnormalities and severe hypersensitivity reactions.

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The timetable you submitted on January 21, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 31, 2013
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	March 31, 2015
	March 31, 2016
	March 31, 2017
	March 31, 2018
	March 31, 2019
	March 31, 2020
	March 31, 2021
	March 31, 2022
Study Completion:	January 31, 2023
Final Report Submission:	September 30, 2023

Submit the protocol to your IND 073193, with a cross-reference letter to this NDA. Submit all interim and final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:
“Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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Center for Drug Evaluation and Research
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METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

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POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Prescribing Information
Medication Guide
Carton and Container Labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH

01/25/2013

EXHIBIT 11

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

TORRENT PHARMACEUTICALS LIMITED and TORRENT PHARMA INC.,

Defendants/Counterclaim-
Plaintiffs.

Civil Action No. 17-3186-SRC-CLW

(CONSOLIDATED)

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

INDOCO REMEDIES LTD.,

Defendant/Counterclaim-Plaintiff.

Civil Action No. 17-7301-SRC-CLW

**OPENING EXPERT REPORT OF DANA FERRARIS, PH.D.
REGARDING THE INVALIDITY OF U.S. PATENT
NOS. 7,807,689; 8,288,539; AND 8,173,663**

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I. INTRODUCTION TO REPORT

1. I submit this expert report pursuant to Federal Rule of Civil Procedure 26(a)(2)(B) on behalf of Defendants, Indoco Remedies Ltd. (“Indoco”) and Torrent Pharmaceuticals Limited and Torrent Pharma Inc. (collectively, “Torrent”) in the above-captioned action.

2. I have been retained by the law firm Seyfarth Shaw LLP (“Seyfarth”) on behalf of Indoco and Pillsbury Winthrop Shaw Pittman LLP (“Pillsbury”) on behalf of Torrent to serve as a consultant and expert witness in this action. I am being compensated for the time I spend working on this matter at my standard rate of \$600 per hour. Neither the nature of my opinions nor the outcome in this matter affects the amount of my compensation. I have no other financial interests in any of the parties to this action.

3. I understand that Indoco has submitted Abbreviated New Drug Application (“ANDA”) No. 209998 to the Federal Drug Administration (“FDA”) for 12.5 mg alogliptin/500 mg metformin and 12.5 mg alogliptin/1 g metformin tablets, and ANDA No. 210002 for 6.25 mg, 12.5 mg, and 25 mg alogliptin tablets (“Indoco’s proposed alogliptin products”) under Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

4. I similarly understand that Torrent has submitted ANDA No. 21-0159 to the FDA seeking approval to commercially manufacture and/or sell a generic version of the pharmaceutical drug product Nesina in the form of oral tablets containing 6.25 mg, 12.5 mg, and 25 mg of alogliptin benzoate (“Torrent’s aloglitpin products”); ANDA No. 21-0160 seeking FDA approval to commercial manufacture and/or sell a generic version of the pharmaceutical drug product Kazano in the form of oral tablets containing 12.5mg of alogliptin benzoate and 500mg/1000mg of metformin hydrochloride (“Torrent’s alogliptin-metformin products”); and ANDA No. 21-0161 seeking FDA approval to commercially manufacture and/or sell a generic

version of the pharmaceutical drug product Oseni in the form of oral tablets containing 12.5mg/25mg of alogliptin benzoate and 15mg/30mg/45 mg of pioglitazone (“Torrent’s alogliptin-pioglitazone products”) (collectively, “Torrent’s proposed ANDA products”).

5. It is my understanding from counsel that Plaintiffs Takeda Pharmaceutical Co., Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Ltd. (collectively “Takeda”) have asserted that Indoco’s proposed alogliptin products and Torrent’s proposed ANDA products will infringe claims 1, 3, 4, 9, 11-12, 43, and 49 of U.S. Patent No. 7,807,689 (“the ’689 patent”); claims 2-3, 5-7, 9, 11, 15, and 18 of U.S. Patent No. 8,288,539 (“the ’539 patent”); and claims 1, 4, 6-8, 10, 12, 14-17, 19-21, 27, and 29 of U.S. Patent No. 8,173,663 (“the ’663 patent”).

6. I understand that the ’689, ’539 and ’663 patents claim priority to U.S. Provisional application 60/553,571, which was filed on March 15, 2004, and U.S. Provisional application 60/629,524, which was filed on November 18, 2004. Accordingly, I understand that the priority date for the ’689, ’539 and ’663 patents is March 15, 2004. However, even if the priority date is determined later by a court to be November 18, 2004 (*i.e.*, the filing date of the ’524 Application) my conclusions on invalidity would be unaffected for all the reasons discussed herein.

7. This report discloses the analysis I have performed on behalf of Indoco and Torrent to determine whether the asserted claims are valid or not under 35 U.S.C. § 103(a). As explained in detail below, it is my opinion that the asserted claims of the ’689 patent, the ’539 patent, and the ’663 patent are not valid and are obvious under 35 U.S.C. § 103.

8. In arriving at my opinion, and in connection with preparing this report, I have relied on both my own experience, expertise and knowledge in the field and also the materials and references listed in Exhibit A, including the ’689, ’663, and ’539 patent specifications

themselves and portions of their prosecution histories. As this case progresses, I may review additional information. I reserve the right to make any edits to the list of materials in Exhibit A, including the right to delete, add, or clarify the materials listed.

II. QUALIFICATIONS AND EXPERIENCE

A. Education and Training

9. I am currently the Chair of the Department of Chemistry at McDaniel College. Since 2015 I have been a member of the faculty of the Department of Chemistry at McDaniel College. I was formerly a visiting professor of Chemistry at Stevenson University.

10. From 1999-2009, I worked as a senior scientist and principal scientist on drug discovery projects at various pharmaceutical companies, including Guilford Pharmaceuticals, MGI Pharma, and Eisai Pharmaceuticals.

11. From 2009-2014, I worked as a principal scientist at John Hopkins University Brain Science Institute Neurotranslational Drug Discovery Program.

12. I have received several awards and honors including the Ernest M. Marks Award for excellence in chemical research at Johns Hopkins University, and Ira G. Zepp Teaching Enhancement Grant.

13. I am currently the President of the Maryland Section of the American Chemical Society (“ACS”). I have been a member of ACS since 1994, in which time I have held various positions in the organization, including Associate Member of the Budget and Finance Committee, Member of the Committee on Economic and Professional Affairs, and Councilor of the Maryland Section.

14. I am a named co-inventor on 8 issued U.S. patents.

15. I received my B.A. in Biochemistry from the Lafayette College in 1994, a Ph.D. in Organic Chemistry from Johns Hopkins University in 2000, and a MBA from Carey Business School of Johns Hopkins University in 2009.

16. My Current research focuses on two oncology-based medicinal chemistry projects. The first of which involves the design and synthesis of inhibitors of members of the poly(ADP-ribose) polymerase (PARP) superfamily of enzymes. Two recent publications in my labs have outlined the design and synthesis of selective inhibitors of PARP10 and PARP14. The inhibitors designed in my labs have served as tool compounds to decipher the roles of these two enzymes in oncology and virology. The other project involves the design and synthesis of bis-naphthoquinones as potential agents against acute myeloid leukemia. Compounds developed in my labs have been the basis of a patent and two publications.

17. I have authored and co-authored more than 50 peer reviewed articles the majority of which are directly related to medicinal chemistry projects in which I was an active member. I would consider myself an expert on several of these projects including: PARP (10 publications, 1 review, 1 book chapter), GCPII (7 publications, 1 review), DAAO (5 publications, 1 review), **DPP4 (3 publications, 1 review)**, and Glutaminase (6 publications).

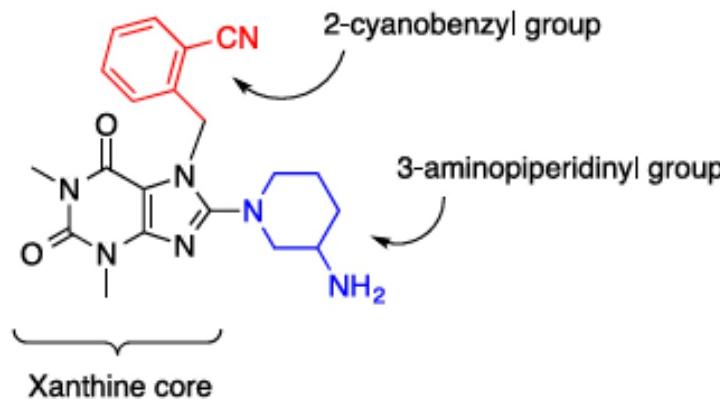
18. I have included a copy of my CV as Exhibit B. This summarizes my education, work experience, publications and presentations, and accolades as of the date of this report's filing.

B. Prior Testimony

19. In the last four years, I have not testified as an expert either at trial or by deposition.

III. SUMMARY OF MY OPINIONS

20. It is my opinion that a person of ordinary skill in the art would have found subject matter of each asserted claim of the '689 patent invalid as obvious in view of the prior art. My opinion is based on the fact that prior to the filing of the '689 patent (*i.e.*, prior to March 2004) both Boehringer Ingelheim and Novo Nordisk identified DPP-IV inhibitors that are structurally homologous compounds to alogliptin as documented in the International Publications WO 2002/068420 A1 and WO 2003/004496 A1 respectively. Indeed, Boehringer Ingelheim and Novo Nordisk each independently disclosed the following compound in their respective patent publications:



The above compound was reported to be biologically active ($IC_{50} = 10 \text{ nM}$) as a DPP-4 inhibitor. This compound is structurally homologous to alogliptin (e.g., the xanthine core in the above compound is replaced with a uracil core in alogliptin). Therefore, in my opinion this compound would have been a natural starting point (*i.e.*, a lead compound) to a person of ordinary skill in the art for further drug development. Moreover, at the time of filing of the '689 patent, the crystal structure of DPP-IV enzyme, and their active sites were known in the prior art. Certainly, with knowledge of the crystal structure and the active sites of DPP-IV enzyme, replacing the xanthine core from the biologically active compound with a uracil core would have

been an obvious consideration to a person of ordinary skill in the art. Indeed, to my knowledge as a medicinal chemist the substitution of such ring cores in drug design and development was known at the time, for instance both U.S. Patent Nos. 5,142,051 and 5,780,476, include uracil and xanthine as preferred interchangeable heterocyclic ring cores.

21. It is my opinion that a person of ordinary skill in the art would have found subject matter of each asserted claim of the '539 patent invalid as obvious. I understand that alogliptin falls within genus of compounds claimed in each of the asserted claims. For the reasons set forth herein, because the species, alogliptin, is obvious (as summarized above), it is my opinion that the claims covering alogliptin generically (*i.e.*, claims 2-3, 5-7, 9, 11, 15, and 18 of the '539 patent) would also have been obvious.

22. It is my opinion that a person of ordinary skill in the art also would have found subject matter of each asserted claim of the '663 patent invalid as obvious. Alogliptin falls within the genus of compounds referred to in each of the asserted claims of the '663 patent. Since alogliptin is a DPP-IV inhibitor, the use of alogliptin, stereoisomers of alogliptin, and pharmaceutically acceptable salts of alogliptin for the treatment of type II diabetes is obvious. Therefore, the genus claims that incorporate alogliptin and related compounds, and their salts (*i.e.*, claims 1, 4, 6-8, 10, 12, 14-21, 27, and 29 of the '663 patent) would also have been obvious.

IV. BACKGROUND OF THE STATE OF THE ART IN MARCH 2004

23. Below, I describe the details of what was generally known in the art as of March 2004.

24. Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled

hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore, patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus (*Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus*, 20(7) Diabetes Care 1183–1197 (Jul. 1997) and Genuth S., et al., *Follow-up Report on the Diagnosis of Diabetes Mellitus*, 26(11) Diabetes Care 3160–167 (Nov. 2003)).

25. Prior to 2004, it was known that there were two generally recognized forms of diabetes: type 1 diabetes and type 2 diabetes. In type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

26. Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet fully understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and

storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

27. Prior to 2004, various treatments for type 2 diabetes were known, and involved the use of various therapeutic agents that acted through different underlying mechanisms of action. For example, it was known that anti-absorptive agents such as α -glucosidase inhibitors (*e.g.*, migitol) reduced the quantity of glucose entering the bloodstream from the intestinal tract; insulin secretagogues such as sulfonylureas and meglitinides (*e.g.*, Daonil®) stimulated the secretion from pancreatic β -cells; insulin sensitizers such as thiazolidinediones and biguanides (*e.g.*, metformin) improved insulin resistance; incretin mimetics (*e.g.*, GLP-1 receptor agonists) activated the glucagon-like peptide 1 (GLP-1) receptor; and dipeptidyl peptidase-IV inhibitors acted by inhibiting the breakdown of GLP-1.

28. It was known prior to 2004, that both the level and the duration of hyperglycemia in type 2 diabetes are closely related to the risk of developing diabetic complications (Stratton, I., *Association Of Glycaemia With Macrovascular And Microvascular Complications Of Type 2 Diabetes (UKPDS 35): Prospective Observational Study,*" 321(7258) Br. Med. J. 405-412 (Aug. 12, 2000)). Therefore, achieving glycemic control is a prerequisite for prevention of cardiovascular and microvascular complications in type 2 diabetes. Lifestyle interventions, including dietary adjustments and increased physical activity, are cornerstones of the therapy. For most patients, however, pharmacological intervention is required and present guidelines suggest metformin to be a first line treatment (Inzucchi, S., *Oral Antihyperglycemic Therapy For Type 2 Diabetes: Scientific Review*, 287(3) JAMA. 360–372 (Jan. 16, 2002) ("Inzucchi")). Metformin is an inexpensive compound with documented glucose-lowering effect in both obese and non-obese subjects with type 2 diabetes (Hundal, R., *Metformin: New Understandings, New*

Uses, 63(18) Drugs 1879–894 (2003) (“Hundal”)). Hypoglycemia is rarely seen during metformin therapy, and the potential fatal adverse event of lactic acidosis is uncommon; nevertheless, caution should always be exercised when treating subjects with renal insufficiency with metformin. In spite of the beneficial effects of metformin in improving glycemic control, very often, however, metformin alone is insufficient for achievement of good metabolic control. Often, also, glycemic control deteriorates in metformin-treated patients. This necessitates combination therapy by adding a secondary compound to metformin. Most often, sulphonylureas are added (Inzucchi at 361-364). The rationale for this combination is that sulphonylureas stimulate insulin secretion, which is a complimentary mechanism to the improvement in insulin sensitivity by metformin. Other combinations with metformin include thiazolidinediones and insulin (Setter, S. et al., *Metformin Hydrochloride In The Treatment Of Type 2 Diabetes Mellitus: A Clinical Review With A Focus On Dual Therapy*, 25(12), Clin. Ther. 2991–3026 (Dec. 2003)).

29. The rationale for the development of DPP-4 inhibitors for use in the treatment of type 2 diabetes relies on augmentation of the incretin effect (Holst, J., et al., *Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes*, 47(11) Diabetes 1663–670 (Nov. 1998)). The two most important incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). GLP-1 inhibits glucagon secretion, delays gastric emptying, and induces satiety (Gutzwiller, J. et al., *Glucagon-Like Peptide-1 Promotes Satiety And Reduces Food Intake In Patients With Diabetes Mellitus Type 2*, 276(5) Am. J. Physiol. R1541–4 (May 1999)). In addition, at the time it was shown that the development of GLP-1 as a therapy has, however, been complicated by its rapid inactivation, which is due to removal of the two N-terminal residues by DPP-4, which inactivates GLP-1

(Mentlein, R., *Dipeptidyl-Peptidase IV (CD26)--Role In The Inactivation Of Regulatory Peptides.* 85(1) Regul Pept. 9–24 (Nov. 30, 1999)). To overcome this, medicinal chemists focused their research on the development of inhibitors of DPP-4, which prevent the inactivation of GLP-1 and thereby enhance and prolong the action of the endogenous incretin hormone. DPP-4 inhibition also prevents the inactivation of the other incretin hormone, GIP, and therefore the concentrations of the active form of this hormone are also increased during DPP-4 inhibition. The first proof-of-concept study of DPP-4 inhibition showed improved metabolic control with reduced fasting and prandial glucose levels and reduction of HbA1c after 4 weeks of treatment of the DPP-4 inhibitor, NVP-DPP728 (Ahrén, B. et al., *Inhibition Of Dipeptidyl Peptidase IV Improves Metabolic Control Over A 4-Week Study Period In Type 2 Diabetes*, 25(5) Diabetes Care 869–875 (May 2002) (“Ahrén”)).

30. Since the early 1980s, medicinal chemists employed structure-based drug design to develop and identify inhibitors that lead to therapeutic drugs (Anderson, A., *The Process of Structure-Based Drug Design*, 10(9) Chem. & Bio. 787-797 (Sept. 2003)). The structure-based drug design approach involves modifications to direct a candidate small molecule toward inhibition of an enzyme based on the structural information on the protein-ligand or enzyme-substrate complexes, including, for example, interactions of the substrate with the target site (catalytic site or active site) of the enzyme/protein, which were usually disclosed in the co-crystallization studies where the enzyme/protein is crystallized with an initial substrate. (*Id.* at 790). Interactions between protein and ligands typically involve hydrogen bonding, hydrophobic interactions, and/or other noncovalent interactions such as $\pi-\pi$ stacking (also known as pi stacking i.e., the noncovalent interactions between aromatic rings). (*Id.*; see also McGaughey, G. et al., *Pi-Stacking Interactions. Alive and Well in Proteins*, 273(25) J. Bio. Chem. 15458–

463, 15458 (Jun. 1998) (“McGaughey”).)

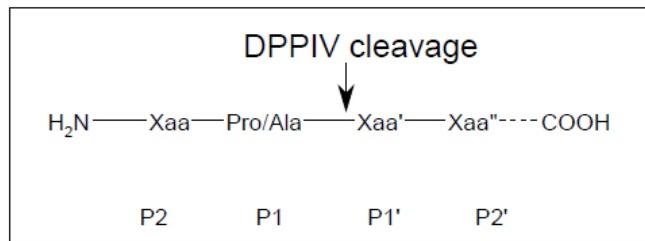
31. At the time of the invention, scaffold hopping was one of the known structure-based approaches for new drug design. (Böhm et al., *Scaffold Hopping*, 1(3) Drug Discovery Today: Technologies 217-223, 217-218 (Dec. 2004) (“Bohm 2004”))¹. Prior to 2004, scaffold hopping had been successfully used in many important new drug discoveries, particularly in the cases where one was seeking to develop non-peptidic small molecules rather than peptidic ligands. (*Id.* at 218.) The scaffold hopping approach was based on the observations that structurally different chemical structures can bind to the same target if such chemical structures maintain some essential features of the pharmacophore - an existing chemical structure displaying the desired biological activity. (*Id.* at 217.) Scaffold hopping often uses the key interaction centers and the active site shape as constraints so that it maintains the key features, i.e., molecular recognition between the protein/enzyme and ligand/substrate. As a result, the method makes use of available crystal structures of protein-ligand or enzyme-substrate complexes. (*Id.* at 222.)

32. The motivation to use scaffold hopping to develop novel compounds was within the purview of one of ordinary skill in the art at the time of the invention for at least these reasons: 1) a replacement in the scaffold can lead to an improved binding affinity; 2) a replacement in the scaffold can improve the solubility of the compound. (*Id.* at 218); and 3) a change in the central scaffold can lead to a novel structure that satisfies at least one criteria of patentability i.e. novelty, particularly when the starting small molecule (lead compound) has

¹ While Böhm was published in December 2004, i.e., after March 2014, the reference reviews examples of scaffold hopping prior to that date and provides evidence of the knowledge that one of ordinary skill in the art would have had at the time of the patent filings at issue in this case. (See Böhm 2004 at 217-218, 222.)

already been patented.

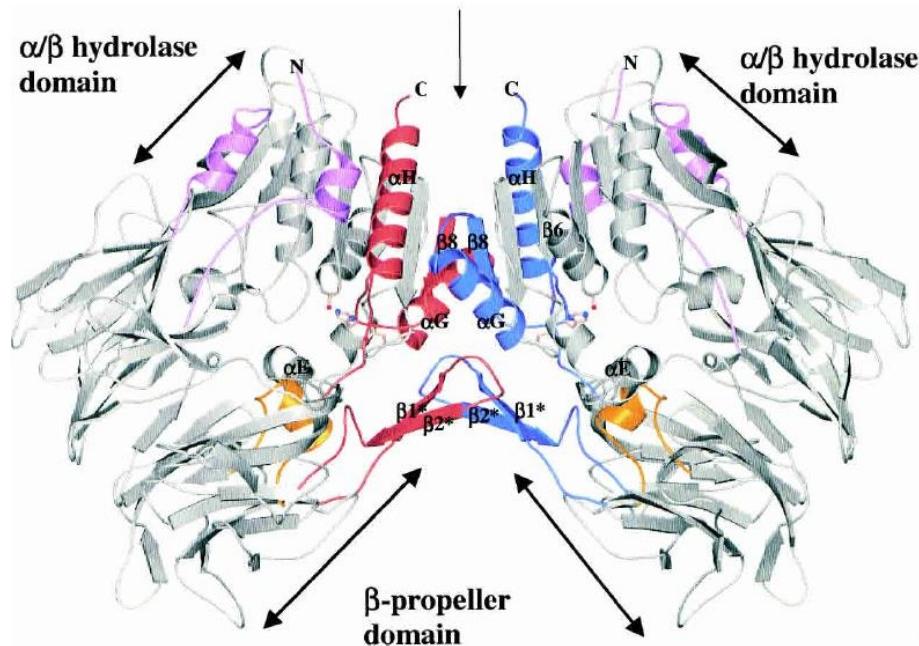
33. DPP-IV is a serine protease that cleaves preferentially Xaa-Pro (Xaa represents any amino acid), and to a lesser extent, Xaa-Ala dipeptides from the N-terminal end of oligopeptides with typical length of 30 aa. The P1, P2 positions² are depicted schematically below. (See Wiedeman, P. et al., *Dipeptidyl Peptidase IV Inhibitors For The Treatment Of Impaired Glucose Tolerance And Type 2 Diabetes*, 4(4) Current Op. Investigational Drugs 412-420 (Apr. 2003), at 413-14 (“Wiedeman”).) The corresponding binding subsites on the enzyme (DPP-IV) are called S1, S2 and S1', S2'... Sn'. (Lambeir, A., *Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV*, 40(3) Crit. Rev. Clin. Lab. Sci. 209-294, 216. (Jun. 2003) (“Lambeir”)).



34. The biologically active form of DPP-IV exists as a dimer with two domains, an α/β hydrolase domain and an eight-bladed propeller domain as shown in the ribbon diagram below. (Aertgeerts, K., et al., *Crystal Structure Of Human Dipeptidyl Peptidase IV In Complex With A Decapeptide Reveals Details On Substrate Specificity And Tetrahedral Intermediate Formulation*, 13(2) Protein Sci. 412-421, 413-414, Figure 1 (Feb. 2004), “Aertgeerts”). Two

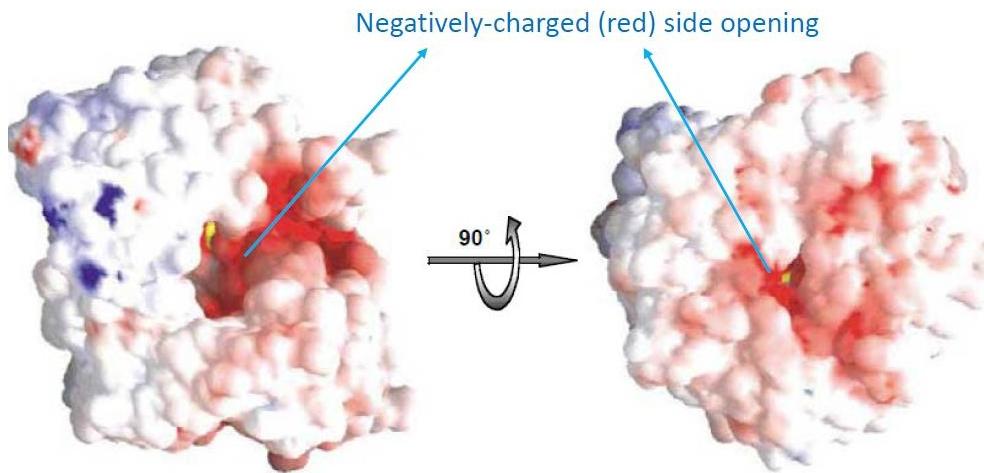
² Under the common nomenclature, residues in a peptide substrate are called P1, P2, and P1', P2', P3'... Pn' counting from the scissile bond toward the N- and C- terminus of the peptide, respectively. (See Lambeir, A., *Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV*, 40(3) Crit. Rev. Clin. Lab. Sci. 209-294, 216 (Jun. 2003).)

openings access the cavity, a funnel shaped opening through the β -propeller and a larger opening between the hydrolase and propeller domains.



35. Both openings are negatively charged (as illustrated in the figure³ below), which attracts the positively charged amine found in *all* inhibitors. (Wiedeman at 418.) It was reported that the substrate may access the DPP-IV enzyme via a side opening formed at the interface of the β -propeller and hydrolase domains. (Aertgeerts at 414.)

³ In this figure, the surface of a DPP-IV molecule (not the dimer) was colored by electrostatic potential. The negatively charged surface is red and positively charged surface is blue, viewed from the side and the bottom of the β -propeller. The yellow is a DPP-IV inhibitor (Val-Pyr). (See Rasmussen H., et al., *Crystal Structure of Human Dipeptidyl Peptidase IV/CD26 in Complex with a Substrate Analog*, 10(1) Nat. Struct. Biol. 19-25, 20, Fig. 1.c. (Jan. 2003).)



36. Prior to 2004, the crystal structures of human DPP-IV as well as its co-crystallization with various substrates were well known in the art. For example, Aertgeerts and Engel, M., et al., *The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism*, 100(9) PNAS 5063-068 (Apr. 29, 2003) (“Engel”) both describe the crystal structures of DPP-IV and its structural features that underlie the substrate recognition and binding of DPP-IV.

37. The crystal structures in the prior art disclose the detailed understanding of the molecular mechanisms that determine the interactions of the substrate with the residues present at the active site of DPP-IV. First, two essential glutamic acid residues, E205 and E206, form a salt bridge (a combination of two noncovalent interactions: hydrogen bonding and ionic bonding) to an amine group in the inhibitor, and this interaction is responsible for orienting the peptide/substrate for cleavage. (Wiedeman at 418; Aertgeerts at 415.) Second, a well-defined hydrophobic pocket forms the S1 binding site for proline/substrate recognition and determines the binding specificity of the substrate. The hydrophobic S1 pocket is lined by residues Val 656, Tyr 631, Tyr 662, Trp 659, Tyr 666, and Val 711. Third, the S2 pocket is hydrophobic and determined by the side chains of Arg 125, Phe 357, Tyr 547, Pro 550, Tyr 631, and Tyr 666.

Other binding sites (such as the S1', S2' binding sites) are not well defined and thus less important.

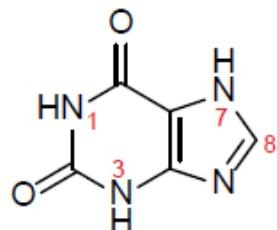
38. Another essential element for DPP-IV activity is Ser 630, which is located on the “nucleophilic elbow” formed by residues Gly-Trp-Ser630-Tyr-Gly. The hydroxyl group of the serine residue (S630) moves significantly to optimally interact with the carbonyl bond of the scissile bond when binding to the substrate. (Aertgeerts at 416.) Aertgeerts also reports that the availability of the DPP-IV/substrate structure “will assist in the rational design of highly specific and potent inhibitors that can be used to better understand the role of DPP-IV, and as potential treatments for diabetes and related disorders.” (*Id.* at 418.) At the time of invention, computational tools had been developed to use the known crystal structure of the target protein (such as DPP-IV) and search for the right structure fragment to modify the existing inhibitor compound and design for the novel scaffold. (Bohm at 222-223.)

39. One of ordinary skill in the art at the time of the invention would have understood the protein-substrate binding interactions in general. For example, McGaughey describes analysis of the high-resolution x-ray crystal structure of several proteins to study the primary interactions between the aromatic side chains of the amino acids Phe, Tyr, His, and Trp. (McGaughey at Abstract.) McGaughey reports that pairs of aromatic side chain amino acids preferentially align their respective aromatic rings in an off-centered parallel orientation called “π-stacking.” (*Id.*)

40. Generally, DPP-IV inhibitors are classified into two main categories, dipeptide like and nonpeptidic inhibitors. (Evans, D., *Dipeptidyl Peptidase IV Inhibitors*, 5(6) IDrugs 577-585 (Jun. 2002) (“Evans”); Wiedeman at 417.) Dipeptide-like inhibitors are inhibitors that mimic the substrates. Because the pyrrolidine ring of proline provides a strong recognition

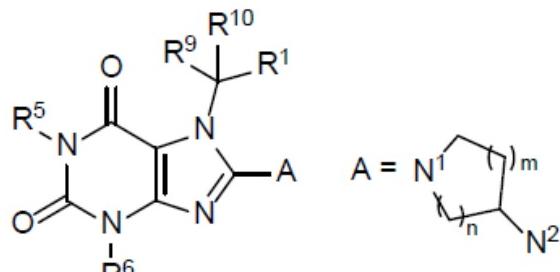
element for DPP-IV substrates, many of the dipeptide-like inhibitors incorporate a pyrrolidine ring. (Wiedeman at 414). In the dipeptide-like class of DPP-IV inhibitors, 2-cyanopyrrole was reported as an important structural element in a large number of DPP-IV inhibitors because the cyano group at the 2-position on the pyrrolidine acts as “a serine ‘hook’ forming an imidate with the catalytic-site serine” (*i.e.*, S630) thereby contributing to the excellent potency of the inhibitors. (*Id.*)

41. Among the non-peptidic class of DPP-IV inhibitors known at the time of the invention, the compounds having a xanthine core (structure shown below), discovered by two companies (Novo Nordisk and Boehringer Ingelheim) independently, were found to have the desired DPP IV inhibitory activity. (Wiedeman at 417.)



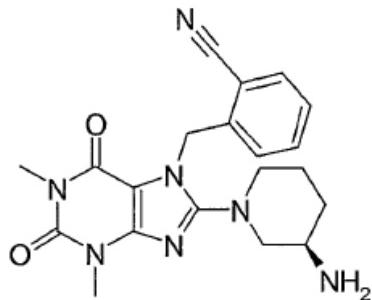
xanthine

42. For example, Kanstrup *et al.*, WO 03/004496 entitled DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes, published January 16, 2003 (“the WO ’496 publication”), filed by Novo Nordisk, discloses xanthine-based non-peptidic DPP-IV inhibitors with the general structure of Formula I below. (WO ’496 publication at Abstract). Specifically, the WO ’496 publication discloses that a cyclic diamine attached to the 8-position of the purine skeleton are “potent and selective inhibitors of DPP-IV” and can be used for treatment of Type 2 diabetes. (*Id.* at 2, ll. 23-29; at 7, ll. 1-3).



Formula I

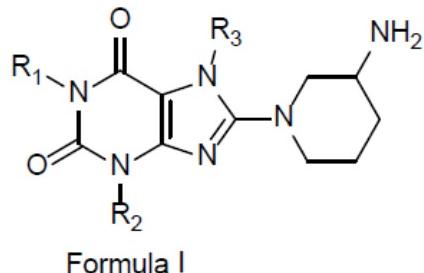
43. Notably, many of the working examples from the WO '496 publication teach DPP-IV inhibitors having 3-aminopiperidinyl group attached to position 8, with R-enantiomer at the amino group as the preferred configuration at the amino group. Indeed, the compound of Example 1 and that of Example 16 of the WO '496 publication, contain 2-cyanobenzyl and aminopiperidinyl groups on the adjacent 7 and 8 positions of the xanthine scaffold, as illustrated in the following structure:



Example 16 of Kanstrup 2003

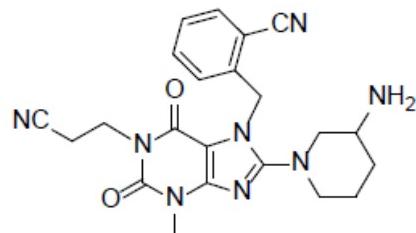
44. Shortly after the WO '496 publication's disclosure, C.A. Patent No. 2,496,249 to Mark *et al.*, entitled "8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments," published on March 4, 2004 ("Mark 2004"), filed independently by Boehringer Ingelheim, also discloses various xanthine-based DPP-IV inhibitors with a 3-aminopiperidinyl group attached to position 8 of the xanthine core as shown in Formula I below.

(Mark 2004 at Abstract.) Mark 2004 discloses that many of these compounds exhibit high potency in inhibiting DPP-IV activity expressed as IC₅₀ values ranging from 1 nm to 10 nm. (*Id.* at 33-35.).



Formula I

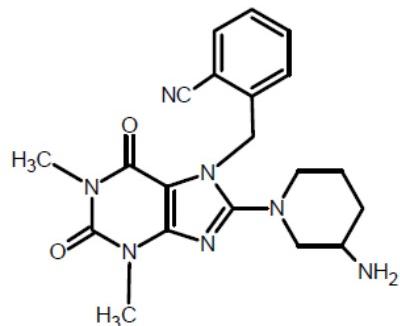
45. Mark 2004 also discloses various xanthine-based compounds with both a cyano group (2-cyanobenzyl at position 7 and cyanoethyl in position 1 of the xanthine scaffold) and 3-aminopiperidinyl group at position 8 of the xanthine scaffold. (*Id.* at 135-185, compounds (Example Nos. 1(1), 1(121), 2(4), 2(9), 2(10), 2(11), 2(12), 2(14), 2(17), 2(90), 2(115), and 2(263)).) For example, compound 1(1) has the following formula structure:



Compound 1(1)

46. The compounds of Examples 2(12) and 2(17) disclosed in Mark 2004 containing both 2-cyanobenzyl and 3-aminopiperidinyl groups exhibit DPP-IV inhibitory activity at IC₅₀ values of 16 nM and 32 nM, respectively. (See CA 2 946 249 at 34, 137, 138). In addition, the same research group from Boehringer Ingelheim had previously reported in a separate reference the potency of compound **1(121)** (1,3-dimethyl-7-(2-cyanobenzyl)-8-(3-aminopiperidin-1-yl)-

xanthine containing both 2-cyanobenzyl and 3-aminopiperidinyl groups (structure shown below) as IC₅₀ value of 10 nM. (See CA '730 at 99, 197.)



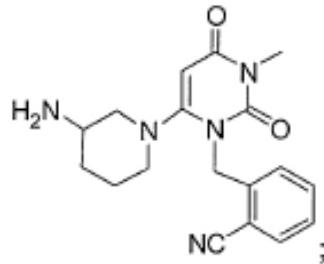
Compound 1(121)

47. Thus, the state of the art at the time of the invention had revealed that both the cyano group (as the 2-cyanobenzyl) and the 3-aminopiperidinyl group are important structural elements that lead to great inhibitory potency against DPP-IV.

V. THE PROSECUTION HISTORIES OF THE PATENTS AT ISSUE

A. Prosecution History of the '689 Patent

48. I have been provided the following information relating to the prosecution of the patents at issue in this litigation. With respect to the '689 patent, U.S. Application No. 11/080,992 ("the '992 application") was originally filed with 161 claims. ('689 Patent File History, at Claims dated March 15, 2005.) On June 19, 2007, the Examiner issued a restriction requiring an election by the Applicant as between two groups of claims. (Office Action dated June 19, 2007, at 2-6.) In response to the restriction requirement, the Applicant amended claim 1 to specifically relate to compound of the formula below. (See July 19, 2007 Amendment, at 2, 2.5) The Applicant cancelled claims 2-161 and added claims 162-276. (*Id.* at 3-24.)



49. On August 8, 2007, the Applicant filed a Preliminary Amendment amending claims 165, 168, 169, 172, 179, 185, 193, 195, 201, 205, and 260 prior to the examination. (August 8, 2007 Preliminary Amendment at 3-23.) On October 16, 2007, the Examiner withdrew the restriction requirement, but rejected claims 1 and 162-276 under 35 U.S.C. § 112, ¶ 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention because the terms “esters,” “tautomers,” and “prodrugs” are not clear. (*See* Non-Final Rejection dated October 16, 2007, at 3-4.) Claims 162, 163, 166, 167, 170 and 171 were rejected for not further limiting the claim (*i.e.*, claim 1) from which they depend identifying that claim 1 did not recite stereoisomers. (*Id.* at 4.) In response, the Applicant amended claims 1 and 162-276 to delete reference to “esters,” “tautomers,” and “prodrugs.” (January 14, 2008 Amendment, at 1-21.) Claims 1 and 165, 169, 173, 191, 197 and 214 were also amended to recite “including all stereoisomers ... thereof.” (*Id.*) The Examiners also rejected claims 1 and 162-276 under 35 U.S.C. § 112, ¶ 1 for lack of enablement indicating that the specification does not reasonably provide enablement for making solvates. (Non-Final Rejection dated October 16, 2007, at 7-8.) In response, the Applicant amended claims 1, 164, 165, 168, 169, 172, 173, 179, 185, 191, 193, 195, 197, 201, 205 and 214 to delete reference to esters and polymorphs and references to prodrugs and solvates. (January 14, 2008 Amendment, at 1-21.)

50. The Examiner did not find the Applicant’s argument persuasive and maintained

rejection of claims 1, 162-208, 214-216, 218-225, 231-233, 235-242, 248-250 and 252-276 as being indefinite and rejection of claims 160-276 as lacking enablement. (Final Rejection dated April 11, 2008 at 2-28.) The Examiner also rejected claims 197-208 as being substantial duplicates of claims 191-196. (*Id.* at 28-29.) In response, the Applicant canceled claims 191-196, 218-225, 235-242, and 252-259 and amended claims 1, 164, 165, 169, 173, 197, 214, and 215 to recite “or stereoisomers ... thereof” and “or pharmaceutically acceptable salts thereof.” (July 11, 2008 Amendment, at 16-17.) The Applicant also amended claims 260 and 273 to delete reference to polymers, solvates, esters, tautomers, enantiomers and prodrugs, and amended claims 216, 233 and 250 to recite only “breast cancer.” (*Id.*)

51. The Examiner withdrew the finality of the Final Office Action, but still rejected all the pending claims. (August 19, 2008 Non-Final Rejection at 2-3.) Specifically, the Examiner rejected claims 173-190 as being indefinite, claims 197-208 as lacking enablement, and claims 1 and 162-190 were rejected as allegedly being anticipated by Schilling et al. (CA 143:347172, 2005) (*see also*, U.S. Patent No. 7,304,086 and U.S. Patent No. 7,371,871). (*Id.*). In response, the Applicant amended claims 173, 179 and 185 to recite that the pharmaceutical composition includes “one or more compounds selected from the group consisting of excipients, diluents, lubricants, binders, adjuvants, carriers, wetting agents, emulsifying agents, solubilizing agents and pH buffering agents.” (November 19, 2008 Amendment at 16.) The Applicant argued that the disclosure relied upon by the Examiner was derived directly from Applicant’s own work and dated after the earliest priority date of the pending application, and it only refers to the claimed compound alogliptin using their internal registration number “SYR-322.” (*Id.* at 17.)

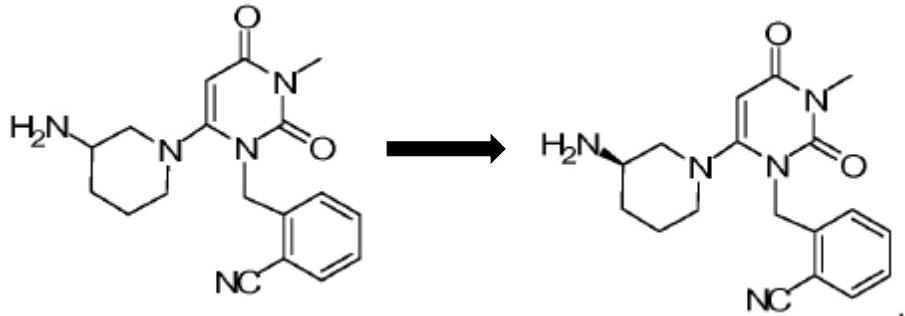
52. The Examiner maintained the rejection over claims 197-208 under 35 U.S.C.

§ 112, ¶ 1 for lack of enablement. (Non-Final Rejection dated January 9, 2009 at 2.) The Examiner also rejected claims 1 and 162-190 under 35 U.S.C. §102(e) as being anticipated by Schilling et al., CA 143: 347172 (2005), US 7,304,086, and WO 2005/075436; and rejected claims 1, 162-190, 197-208, and 260-276 under 35 U.S.C. § 103(a) as being obvious over Schilling et al., CA 143: 347172 and WO 2005/075436. (*Id.* at 19-20.) In response to the lack of enablement rejection, the Applicant amended claims 199, 203 and 207 to recite that the article of manufacture may comprise a label indicating “a disease state for which the compound is to be administered wherein the disease state is diabetes.” (April 9, 2008 Amendment at 16.) In response to the anticipation rejection, the Applicant argued that the teaching of SYR-322 did not appear in the priority document relating to WO 2005/075436 until February 4, 2005, which is later than the priority date for SYR-322 (March 15, 2004). (*Id.* at 16-17.)

53. The Examiner found the Applicant’s argument unpersuasive and maintained the rejection under 35 U.S.C. §§102(e) and 103(a). (See Non-Final Rejection dated August 7, 2009 at 2-5.) The Examiner also rejected claims 1, 162-190, 197-208, 214-216, 231-233, 248-250 and 260-276 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 25-32, 34-39, 43, 49-54, 72-76, 78-83 and 87 of co-pending Application No. 11/928,944. (*Id.* at 6.) In response, Applicant cancelled claims 260-276. (November 9, 2009 Amendment at 11.) With respect to the rejection under 35 U.S.C. §§ 102(e) and 103(a), Applicant argued that “Schilling’s disclosure of ‘SYR-322’ is after Applicant’s priority date for the pending claims” and neither Schilling nor CA 143: 347172 is prior art. (*Id.* at 14-15.)

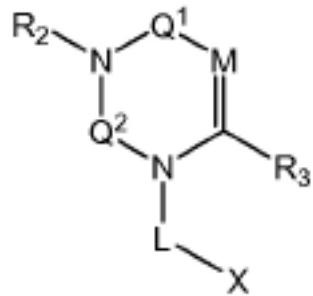
54. On February 24, 2010, a notice of allowance was issued to the then pending claims 1, 162-190, 197-208, 214-216, 231-233, and 248-250. On February 22, 2012, Applicant submitted a Request for Certificate of Correction to correct the structure recited in claims 4, 12,

19, 25, 35 and 39 to show the stereochemistry for the 3-aminopiperidinyl group:



B. Prosecution History of the '539 Patent

55. U.S. Patent Application 11/929,482 ("the '482 Application") was originally filed with 161 claims. ('589 Patent File History, at Claims dated October 30, 2007.) On November 15, 2010, the Examiner issued a restriction requiring an election by the Applicant as between two groups of claims. (Office Action dated November 15, 2010, at 2-6.) In response to the restriction requirement, the Applicant amended claim 1 to recite a genus of compounds of the formula below (genus encompassed alogliptin). (See Amendment dated December 15, 2010, at 2.)



56. On May 3, 2011, the Applicant filed an Amendment in response to a non-final office action, amending claims 1 and 51 to overcome prior art rejections under 35 U.S.C. §§ 102

and 103. The Applicants also cancelled claims 2, 23, 25, 27, 36-42, 44, 45, 52-54, and 63-156. The Applicant also filed terminal disclaimers to overcome obviousness type double patenting rejections. (Amendment dated May 3, 2011.) On August 5, 2011, the Examiner issued a final rejection rejecting the pending claims as being indefinite and also for obviousness-type double patenting. (*See* Final Rejection dated August 5, 2011.) The Applicants responded on November 4, 2011, by deleting the terms “imine group, sulfonyl group, and sulfinyl group” from the variable groups R₂, R₄, etc., and submitting terminal disclaimers. (Amendment dated November 4, 2011.) On November 21, 2011, the Examiner issued an advisory action, and in response, the Applicants filed a Request for Continued Examination on December 13, 2011. Further, the Examiner issued a non-final office action on February 3, 2012, maintaining the obviousness type double patenting rejection because the previously filed terminal disclaimers were not properly executed. (*See* Non-final Rejection dated February 3, 2012). The Applicants filed a response to the non-final office action on March 30, 2012 by filing terminal disclaimers over three U.S. patents to overcome the obviousness-type double patenting rejection.

57. On June 14, 2012, a notice of allowance was issued allowing claims 1, 24, 26-28, 35, 43, 46-51, 55-62, and 157-161. (*See* Notice of Allowance dated June 14, 2012).

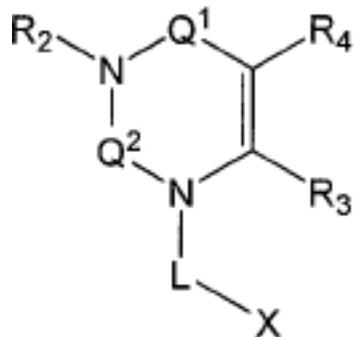
58. On March 25, 2013, Applicants submitted a Patent Term Extension Application Under 35 U.S.C. § 156. On May 18, 2016, the United States Patent and Trademark Office mailed a Notice of Final Determination awarding the '539 patent 101 day of patent term extension.

C. Prosecution History of the '663 Patent

59. U.S. Patent Application 11/929,593 ("the '593 Application") was originally filed on October 30, 2007, with 95 claims directed to methods of inhibiting DDP-IV. ('63 Patent File

History, at Claims dated October 30, 2007). On September 9, 2008, the Applicant submitted a preliminary amendment amending certain claims by, inter alia, deleting certain functional groups from the definition of variable groups, and a new claim 96 was added. (*See* Amendment, September 9, 2008, at 9, 11.)

60. In response to a restriction requirement dated September 4, 2009, the Applicant submitted a response on December 18, 2009, by electing group I directed to claims 1-95 and canceling claims 66, 67, and 73. The Applicant further amended the claims by replacing the previously presented Markush structure with the following structural formula:



61. On March 23, 2010, the Examiner issued a non-final office action rejecting the pending claims as being indefinite, lacking enablement, and for obviousness type double patenting. (Office Action dated March 23, 2010.) In response, the Applicant amended the claims by narrowing the scope of the same and submitted terminal disclaimers. (Amendment dated August 23, 2010.)

62. On September 23, 2010, the Examiner issued an office action maintaining the obviousness type double patenting rejection because the previously filed terminal disclaimers were not properly executed. (*See* Final Rejection dated September 24, 2010.) Applicant replied

on November 17, 2010, by submitting terminal disclaimers.

63. On November 30, 2010, the Examiner issued another non-final office action rejecting the claims as being anticipated and obvious. The office action indicated that only claims 91 and 92 were allowable. (Office Action dated November 30, 2010.) In a response dated, May 31, 2011, the Applicant cancelled claims 1-4, 7, 9-39, 41, 50-56, 58-59, 66-67, 73-90, and 96, and amended certain claims by narrowing their scope. (Amendment dated May 31, 2011).

64. On August 26, 2011, a Notice of Allowance was issued allowing claims 5, 6, 8, 40, 42-49, 57, 60-65, 68-72, and 91-95. (*See* Notice of Allowance dated August 26, 2011.)

65. On March 25, 2013, Applicants submitted a Patent Term Extension Application Under 35 U.S.C. § 156. On May 18, 2016, the United States Patent and Trademark Office mailed a Notice of Final Determination awarding the '663 patent 262 days of patent term extension.

VI. CLAIM CONSTRUCTION

66. I understand that the asserted claims of the '689 patent, the '539 patent, and the '663 patent claims are to be given their plain and ordinary meaning as would have been understood from the perspective of one of ordinary skill in the art. All of my opinions are also provided from the perspective of one of ordinary skill in the art.

VII. BASES FOR MY OPINION OF OBVIOUSNESS

A. Relevant Legal Standards

67. I have been provided with the following Basic Legal Standards by counsel for Indoco and Torrent and I have applied these standards in forming my opinions set forth below:

68. **Invalidity.** Under Section 282 of the Patent Act, a patent is presumed valid and the party challenging validity has the burden of proving invalidity by clear and convincing evidence. An invalidity analysis involves two steps. The first step involves ascertaining the proper meaning and scope of the claims. In ascertaining the proper scope and meaning, claims are construed the same way for determining both invalidity and infringement. The second step involves determining whether the limitations of the claims, as properly interpreted, are disclosed or suggested by the prior art.

69. **Person of Ordinary Skill In the Art.** My opinions regarding invalidity of the asserted claims of the '689 patent, '539 patent, and '663 patent should be rendered from the perspective of the hypothetical person having ordinary skill in the art (a "POSA").

70. I understand that in order to assess whether there would have been a reason or motivation to modify the compound known in the prior art to make the compound of the asserted claim with a reasonable expectation of success in the obviousness analysis, I must step backward in time and into the shoes worn by the hypothetical POSA when the alleged invention was unknown (just before it was made), which I understand would be before March 2004.

71. I am informed that this POSA is a hypothetical person that is constructed in a manner where the POSA is presumed to be aware of the state of the art and all of the relevant prior art, and who thinks along the conventional wisdom of those in the art. I am informed that the latter means that the POSA is not an automaton but a person of ordinary creativity. This means the POSA is not simply a pair of hands following directives but presumed to have an understanding of the prior art and its technical implications, as well as the problems faced by those working in the field, and is able to apply common knowledge to attempt to solve a given problem.

72. I have been informed and understand that factors that may be considered in determining the level of ordinary skill in the art may include: (a) type of problems encountered in the art; (b) prior art solutions to those problems; (c) rapidity with which innovations are made; (d) sophistication of the technology; and (e) educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate.

73. Based on my knowledge and experience, it is my opinion in reviewing the claims of the '689 patent, the '539 patent, and the '663 patent and their corresponding specifications that the POSA with respect to the subject matter of the '689 patent, the '539 patent, and the '663 patent is a person with a Ph.D. or an equivalent advanced degree in medicinal chemistry and/or organic chemistry (or a closely related discipline such as pharmaceutical chemistry), having at least several years of relevant practical academic or industrial experience researching and developing drugs and can use knowledge in organic chemistry for designing and synthesizing small molecule drugs such as antidiabetic drugs for treating type 2 diabetes. The POSA could have had a lower level of formal education in medicinal chemistry or organic chemistry if such a person had a higher degree of relevant academic or industrial experience in designing and synthesizing small molecule drugs. This experience and knowledge may come from the POSA's own knowledge and experience, or through access to or guidance from individuals with either doctoral or medical degrees in pharmacy/pharmacology or medicine respectively. I understand that this POSA is presumed to be aware of all the pertinent art at the time of the invention was made. The POSA in my opinion should have no trouble understanding the relevant references in the art and would be able to draw appropriate inferences from them and from those others of skill in the art including those he or she may ordinarily collaborate with on matters.

74. **Obviousness.** A claim is invalid as obvious under Section 103 of the Patent Act

if the differences between the subject matter sought to be patented and the prior art are such that the claimed subject matter as a whole would have been obvious to a person having ordinary skill in the art at the time the alleged invention was made. Obviousness is a question of law based on underlying findings of fact. The following factors must be considered in determining obviousness: (1) scope and content of the prior art; (2) difference or differences, if any, between the claims at issue and the prior art; (3) level of ordinary skill in the art at the time the alleged invention was made; and (4) additional objective considerations, if any, indicating that the alleged invention was obvious or not obvious.

75. **Obviousness Analysis under Section 103(a).** Analysis of whether there are any relevant differences between the prior art and the claimed subject matter is performed from the viewpoint of a person having ordinary skill in the art at the time the alleged invention was made. In analyzing the relevance of the differences between the claims at issue and the prior art, inferences and creative steps a person having ordinary skill in the art would have employed in reviewing the prior art at the time that the alleged invention was made may be taken into account. For example, a claim will be obvious if “all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention.” Manual of Patent Examining Procedure, Ninth Ed., Last Revised January 2018, Section 2143 (citing *KSR Intl. v. Teleflex*, 550 U.S. 398, 416 (2007)).

76. **Reason to Combine.** In an obviousness analysis under Section 103(a) of the Patent Act, one may consider whether there existed an apparent reason at the time the alleged invention was made that would have prompted a person having ordinary skill in the art in the

relevant field to combine the known elements in the way the alleged invention does. This reason may come from the prior art, the background knowledge of one having ordinary skill in the art, the nature of the problem to be solved, market demand, or common sense. It is not necessary, however, that the references be combined for the same reasons as the inventor. If a reason existed at the time the alleged invention was made to combine the elements of the prior art to arrive at the claimed subject matter, this evidence would lead to a determination that the claims at issue were obvious under Section 103(a) of the Patent Act.

77. **Obviousness Determination under Section 103(a).** The determination of whether the claimed subject matter is obvious under Section 103(a) of the Patent Act is based on the perspective of a person having ordinary skill in the art at the time the alleged invention was made. The person having ordinary skill in the art is presumed to know all of the prior art that is reasonably relevant to the subject matter of the claimed alleged invention. The person having ordinary skill in the art is also a person having ordinary creativity who can use common sense to solve problems.

78. **Secondary Considerations.** The obviousness inquiry under Section 103(a) of the Patent Act requires the consideration of secondary factors or objective indicia of non-obviousness. It is Plaintiffs' burden to provide evidence of the secondary factors or objective indicia of non-obviousness, which may include: (i) commercial success (so long as the success has a nexus to or resulted from) the alleged invention claimed in the asserted claims of the '689 patent, the '539 patent, and the '663 patent; (ii) unexpected results; (iii) copying; (iv) failed attempts by others; (v) long-felt, but unmet need; licensing of the alleged invention claimed; and, (vi) praise by those in the relevant art —*i.e.*, the field of medicinal chemistry and drug discovery for the asserted claims of the '689 patent, '539 patent, and '663 patent.

B. The Scope and Content of the Prior Art

79. My opinions regarding the obviousness of the asserted claims of the '689 patent, the '539 patent, and the '663 patent rely on a core set of prior art. For purposes of obviousness, I have been instructed to consider March 15, 2004 as the priority date for these three patents. All of the references discussed below were publicly available before that date.

a. Lead Compound References

80. The primary references for invalidity of the asserted claims of the '689 patent, the '539 patent, and the '663 patent, are the WO '420 publication/ CA '730 patent and the WO '496 publication, which are set forth in the following paragraphs. These references disclose a structurally homologous compound to alogliptin possessing a xanthine core that a person of ordinary skill in the art would have used as the lead compound for further investigation and which render alogliptin as obvious.

81. **The WO '420 publication/ CA '730 patent.** International Publication WO 2002/068420 A1, *Xanthine Derivatives, Production and Use Thereof As Medicament*, was filed February 21, 2002, and published September 6, 2002 (the “WO '420 publication”). Canadian Patent No. CA 2 435 730, Xanthine Derivatives, The Preparation Thereof and Their Use As Pharmaceutical Compositions, (the “CA '430 patent”), issued from the National Phase Application of PCT Application No. PCT/EP2002/001820 (published as WO'420), and is the English language equivalent to the WO '420 publication. Each of the patents is assigned to Boehringer Ingelheim.

82. The WO '420 publication and CA '730 patent are directed to substituted xanthines that exhibit inhibition of DPP-IV. (CA '730, ¶ 57). The reference describes that the compounds have use in preventing or treating, in particular, type I or type II diabetes mellitus.

(*Id.* at 1, 100.) The WO '420 publication and the CA '730 patent describe that the compounds may be resolved into their enantiomers and/or diastereomers using common techniques such as chromatography, fractional crystallization, column separation, recrystallization from an optically active solvent, by reacting with optically active substances to form salts or derivatives and separating such compounds based on physical differences, such as solubility. (*Id.* at 96-97.) The reference also describes converting the compounds into salts. (*Id.* at 97.)

83. Biological properties of 31 compounds were investigated using a DPP-IV assay, according to the reference. (*Id.* at 98-100.) Among the compounds tested and found remarkably high in potency is Compound 1(121), which is discussed in depth later in my report. Toxicity was also examined, with all of the compounds being well tolerated in rats. (*Id.*)

84. The disclosures of the WO '420 publication/CA '730 patent are described in further in the next sections providing my opinions.

85. **The WO '496 publication.** International Publication WO 2003/004496 A1, DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes, was filed June 27, 2002 and published January 16, 2003 (the “WO '496 publication”). The WO '496 publication describes purine derivatives useful for treating diseases “such as type 2 diabetes.” (WO '496 publication at 1:3-7.) The reference discloses salts, including the benzoic acid salt specifically, as potential preparations for the compounds. (*Id.* at 18:25-31.) According to the reference, the invention “extends to all of the stereo isomeric forms of the claimed compounds, as well as the racemates.” (*Id.* at 19:7-8.) The WO '496 publication is assigned to Novo Nordisk.

86. The WO '496 publication provides, as its very first example (Example 1), the xanthine derivative identical to Compound 1(121) of the '420 publication/CA '730 patent. (*Id.* at 37:16-38:10.) While the disclosure of a first example in a patent application may not necessarily

suggest such compound as a “lead compound,” the fact that both Boehringer Ingelheim and Novo Nordisk both identified the exact same compound, and further in the Boehringer Ingelheim reference this compound falls in the group of 5 best compounds based on the potent DPP-IV inhibitory activity exhibited by the compounds in IC₅₀ values ranging between 2 nM and 10 nM. It is indicative that the compounds disclosed independently in the Boehringer Ingelheim and Novo Nordisk reference are highly potent DPP-IV inhibitors, and this observation provides a strong suggestion that such a compound can form a starting point of further research and development efforts. (See WO '496 at 37:16-38:10; and Compound 1(121) in CA '730 patent at cols. 99-100.).

b. **DPP-IV Inhibitor Structure References**

87. One of ordinary skill in the art as of March 2004 would also have been aware of the extensive research that had taken place to identify key structural components necessary for DPP-IV inhibitors. Such references are set forth below. I will at times refer to them collectively as the “Structure References””

88. **Evans.** Evans, D., *Dipeptidyl peptidase IV inhibitors,*” 5(6) IDrugs 577-585 (June 2002) (“Evans”). Evans reviews the patent literature from January 2001 to May 2002, noting that there “has been increased interest in DPP-IV inhibitors since their potential for the treatment of diabetes was identified.” (Evans at 577.) The “review focuses on reversible inhibitors” useful “in the treatment of Type II diabetes,” and covers both “dipeptide-like inhibitors that mimic the preferred substrates” and “non-peptide inhibitors.” (*Id., see also* Evans at 579.) The interest, according to Evans, stems from the fact that “diabetes, in particular Type II diabetes, affects a large and still growing patient population that cannot be adequately treated with existing therapies.” (Evans at 578.)

89. As summarized by Evans, DPP-IV is known to cleave an incretin hormone, GLP-1. (Evans at 577.) GLP-1 is responsible for insulin response to oral glucose and is known to be impaired in Type II diabetes. (*Id.*) DPP-IV inhibitors maintain the levels of GLP-1 by preventing the degradation of GLP-1, leading to “enhanced insulin secretion and improved glucose tolerance.” (*Id.*) Thus, the use of “DPP-IV inhibitors has been proposed as a possible treatment of Type II diabetes.” (*Id.*)

90. Evans further describes the structure-function relationships known for the DPP-IV enzyme. (*Id.*) Evans states that compounds that “take advantage of the required interaction with the serine hydroxyl group of the enzyme” are known to be more potent DPP-IV inhibitors. (*Id.*) The reference identifies that certain electrophilic groups, such as aldehydes or ketones, create stability problems not shown with nitriles. (Evans at 578.)

91. Evans specifically recognizes that “[t]he cyano group is sufficiently electrophilic to interact with the serine hydroxyl, but does not cause stability problems” in reviewing a series of dipeptide-based inhibitors. Non-peptide inhibitors also contain this group. (Evans at 581 and Figure 6.)

92. **Wiedeman.** Wiedeman, P. et al., Dipeptidyl Peptidase IV Inhibitors For The Treatment Of Impaired Glucose Tolerance And Type 2 Diabetes, 4(4) Current Op. Investigational Drugs 412-420 (Apr. 2003) (“Wiedeman”). Wiedeman summarizes “advances in the design of potent and selective small molecule inhibitors of DPP-IV”, and challenges for the development of DPP-IV inhibitors for treating “impaired glucose tolerance” and type II diabetes. (Wiedeman at 412.) Wiedeman explains that providing GLP-1 itself as a treatment for type II diabetes is “impractical” because of its short 1 minute to 1.5 minute half-life. (*Id.*) Wiedeman provides a summary of studies underway for certain DPP-IV inhibitors, including a

study in human type 2 diabetics, all of which showed improved glucose tolerance. (Wiedeman at 413.)

93. Among non-peptidic molecules as DPP-IV inhibitors, Wiedeman highlights xanthines as having “attracted attention.” (Wiedeman at 417.) The reference then specifically notes that “[t]wo companies,” Novo Nordisk and Boehringer Ingelheim, “seem to have independently discovered this class of inhibitors.” (*Id.*) Wiedeman favorably describes the bioavailability and potency of such compounds. (*Id.*)

94. **Lambeir.** Lambeir, A., Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV, 40(3) Crit. Rev. Clin. Lab. Sci. 209-294, 216 (Jun. 2003) (“Lambeir”). Lambeir provides a summary on the DPP-IV enzyme, including its amino acid sequence, structural characteristics, and role in type 2 diabetes. (Lambeir at 209; 214-215.)

95. DPP-IV is a serine peptidase. (Lambier at 211.) “A hydrophobic pocket forms the S1 binding site for proline recognition and a second hydrophobic pockets is formed by the S1’ to S’5 site.” Two glutamate residues are recognized as “essential” for activity. (Lambier at 217.) Lambier further identifies the increase in affinity with the use of a cyano group in DPP-IV inhibitors. (Lambier at 223.)

96. Lambier notes that substrate specificity of DPP-IV has been determined with experiments involving synthetic peptides, natural substrates, and p-nitroanilide analog. (Lambier at 218.).

97. Lambier also discloses that catalysis by DPP-IV is “strongly stereospecific,” requiring specific configurations for activity.

98. Engel. Engel, M., et al., *The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism*, 100(9) PNAS 5063-068 (Apr. 29, 2003) (“Engel”). Engel describes the crystal structures of DPP-IV and its structural features that underlie the substrate recognition and binding of DPP-IV. Engel discloses crystal structure of DPP IV enzyme, and discusses the active and non-active site-directed inhibition strategies of the DPP IV target. Determination of DPP-IV crystal structure and identification of important elements of DPP-IV active site provides an excellent starting point for rational design of DPP-IV inhibitors. (Engel at 5068.)

99. Aertgeerts. Aertgeerts, K., et al., *Crystal Structure Of Human Dipeptidyl Peptidase IV In Complex With A Decapeptide Reveals Details On Substrate Specificity And Tetrahedral Intermediate Formulation*, 13(2) Protein Sci. 412-421 (Feb. 2004) (“Aertgeerts”). Aertgeerts reports the crystal structure of DPP-IV in its free form and in complex with part of a substrate (Neuropeptide Y) known to be involved in the regulation of insulin release. (Aertgeerts at 412, 413.) The crystal structure of DPP-IV reveals that the enzyme has two “channels” through which an inhibitor can access the active sites. (*Id.*) Aertgeerts identifies structural features in the active site that contribute to binding, including the “presence of a Glu motif,” and a “well-defined hydrophobic S1 subsite.” (Aertgeerts at 412.)

100. In describing the DPP-IV enzyme structure, Aertgeerts identifies a hydrophobic S1 pocket and an S2 hydrophobic pocket. (Aertgeerts at 415-416.) “Most side chains can be modeled” into the S1 pocket, but charged residues may cause “unfavorable electrostatic interactions.” (Aertgeerts at 417, 418.) As in the Evans reference, Aertgeerts identifies a serine hydroxyl group in S1 that is essential for activity, noting that the group moves significantly to interact with the substrate. (Aertgeerts at 416.) For the S2 pocket, Aertgeerts explains that the

site “preferentially recognizes large hydrophobic and aromatic side chains.” (Aertgeerts at 417.) Knowledge of the DPP-IV/substrate structure will provide guidance for rational design of highly specific and potent inhibitors of DPP-IV that can be used for the treatment of diabetes and related disorders. (Aertgeerts at 418.)

101. Aertgeerts also notes that DPP-IV inhibitors are currently under investigation in human trials for treating type II diabetes. (*Id.*) The reference explains the role of DPP-IV in regulating plasma glucose levels by control of GLP-1. (*Id.*)

c. **Substitution References**

102. A number of references also would have provided motivation for one of ordinary skill in the art to change the core of the compound identified in the '420 publication/CA '730 patent and the WO '496 publication to the core of alogliptin. These “Substitution References,” as I may refer to them, are:

103. **The '051 patent.** U.S. Patent No. 5,142,051, “N-Phosphonylmethoxyalkyl Derivatives of Pyrimidine and Purine Bases and a Therapeutical Composition Therefrom with Antiviral Activity,” filed July 17, 1987 and issued Aug. 25, 1992 (the “'051 patent”).

104. In discussing the interchangeability of certain heterocyclic compounds, the '051 patent discloses, “[t]he heterocyclic base in compounds of the general formula I may be not only a so-called natural pyrimidine or purine base (uracil, thymine, cytosine, guanine, adenine, hypoxanthine, xanthine) or its substituted derivative, but also a modified base such as an aza, deaza, deoxy or deamino analogue, a 6-alkylpurine, etc.” (See '051 patent at col. 4, lines 41-46.)

105. **The '476 patent.** U.S. Patent No. 5,780,476, “Hydroxyl-Containing Xanthine Compounds,” filed June 6, 1995, and issued July 14, 1998 (the “'476 patent”). According to the

‘476 patent, “[p]REFERRED RING CORES INCLUDE SUBSTITUTED OR UNSUBSTITUTED glutarimide, methylthymine, methyluracil, thymine, theobromine, uracil and xanthine. Exemplary preferred cores include, but are not limited to: 1,3-cyclohexanedione, 1,3-cyclopentanedione; 1,3-dihydroxynaphthalene; 1-methyllumazine; methylbarbituric acid; 3,3-dimethylflutarimide; 2-hydroxypyridine; methyldihydroxypyrazolo[4,3-d] pyrimidine (preferably, 1,3-dimethyldihydroxypyrazolo[4,3-d] pyrimidine); methylpyrrolopyrimidine (preferably, 1-methylpyrrolo [2,3-d] pyrimidine); 2-pyrrole amides; 3-pyrrole amides; 1,2,3,4-tetrahydroisoquinolone; 1-methyl-2,4(1H,3H)-quinazolinedione (1-methylbenzoyleneurea); quinazolin-4(3H)-one; alkyl-substituted (C₁₋₆) thymine; methylthymine; alkyl-substituted (C₁₋₆) uracil; 6-aminouracil; 1-methyl-5,6-dihydouracil; 1-methyluracil; 5- and/or 6-position substituted uracils; 1,7-dimethylxanthine, 3,7-dimethylxanthine; 3-methylxanthine; 3-methyl-7-methylpivaloylxanthine; 8-amino-3-methylxanthine; and 7-methylhypoxanthine.” (See ‘476 patent at col. 3, lines 4-22.)

106. **Davies.** Davies, T.G., et al., *Structure-based design of cyclin-dependent kinase inhibitors*, 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002) (“Davies”). Davies determines that knowledge of the structure of Cyclin dependent Kinase 2 (CDK2) target is key in the design and development of a large number of potent inhibitors. Davies has demonstrated that knowledge of pattern of hydrogen bonds between a known compound containing a purine core and the hinge region of the target can be used to design a new compound containing pyrimidine as the core by recreating the hydrogen bonding in pyrimidine system. The pyrimidine compounds showed more potency than the lead purine compound. (Davies at 127)

d. Stereoisomer References

107. Some of the asserted claims relate to the stereoisomers of alogliptin. The Lead

Compound References explicitly cover stereoisomers. There are also many references that disclose the benefits of single stereoisomers in pharmaceutical drugs as well as the use of mixed enantiomer compounds. Below are some of references that I rely on for my opinions on such claims (the “Stereoisomer References”).

108. **Campbell.** Campbell, D.B., *Stereoselectivity in Clinical Pharmacokinetics and Drug Development*, 15(2) Euro. J. Drug Metabolism & Pharmacokinetics, 109-125 (April 1990) (“Campbell”).

109. **Hutt.** Hutt, A.J., *The Development of Single-Isomer Molecules: Why and How*, 7(4 supp. 1) CNS Spect. 14-22 (2002) (“Hutt”).

110. **Crossley.** Crossley, R., *Chirality and the Biological Activity of Drugs*, CRC Press (1995) (“Crossley”).

111. **Izumi.** Izumi, T., et al., *Pharmacokinetics of Troglitazone, an Antidiabetic Agent: Prediction of In Vivo Stereoselective Sulfation and Glucuronidation from In Vitro Data*, 280(3) J. Pharm. & Experimental Therapeutics, 1392-1400 (March 1997) (“Izumi”).

e. **Salt References**

112. Some of the asserted claims relate to the use of alogliptin in the form of a pharmaceutically acceptable salt, and specifically, a benzoate salt of alogliptin. The Lead Compound references disclose salts of the compounds described, including, in the WO '496 publication, salts relating to benzoic acid.

113. The seminal teaching on pharmaceutically acceptable salts is that of Berge, set forth below. In addition, in March 2004, one of ordinary skill in the art also would have been well aware of how to efficiently develop and analyze pharmaceutical salts as indicated in

Higgins below.

114. **Berge.** Berge, S.M., et al., *Pharmaceutical Salts*, 66(1) J. Pharm. Sci., 1-19 (Jan. 1977) (“Berge”).

115. **Higgins.** Higgins, J.D. & Rocco, W.L., *Pharmaceutical Preformulation*, Today’s Chemist at Work 22-26 (July 2003) (“Higgins”).

C. The ’689 Patent

a. The Claims at Issue in the ’689 Patent

116. I understand that Claims 1, 3, 4, 9, 11-12, 43, and 49 of the ’689 patent have been asserted by Takeda as allegedly infringed.

117. Claim 1 of the ’689 patent depicts the chemical structure for alogliptin and also covers stereoisomers or pharmaceutically acceptable salts of alogliptin.

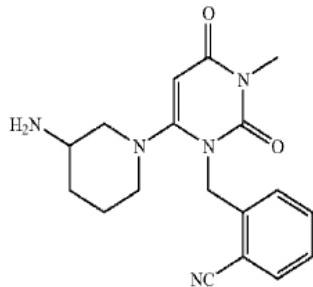
118. Claims 3, 4, 9, and 11-12 of the ’689 patent specify certain salt and stereoisomer forms of alogliptin, and claims 43 and 49 of the ’689 patent cover treatment of Type II diabetes with alogliptin or pharmaceutically acceptable salts or stereoisomers of alogliptin.

119. I have been instructed to assume that, for purposes of obviousness, the priority date for the ’689 patent is March 15, 2004. The references that I rely on, as previously described, are dated before such date.

b. Claim 1 of the ’689 patent

120. Claim 1 of the ’689 patent covers alogliptin or stereoisomers of alogliptin or pharmaceutically acceptable salts of alogliptin.

1. A compound of the formula

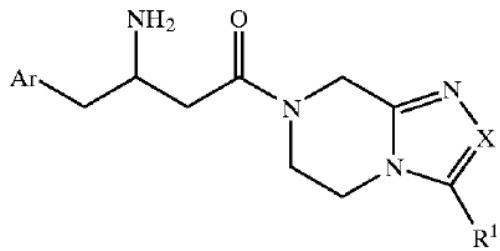


or stereoisomers or pharmaceutically acceptable salts thereof.

121. Claim 1 of the '689 patent is obvious over the CA '730 patent or the WO '496 publication in view of the knowledge of one of ordinary skill in the art as of March 2004, certain references that describe the known structural features of DPP-IV inhibitors (*e.g.*, Evans, Wiedeman, Lambeir, Engel, and/or Aertgeerts (the "Structure References")), and/or references that support substituting a uracil scaffold for a xanthine scaffold (*e.g.*, the '051 patent, the '476 patent and/or Davies (the "Substitution References")).

122. In the early 2000's, researchers were investigating the use of dipeptidyl peptidase-IV enzyme ("DPP-IV") inhibitors because of their potential for the treatment of diabetes, particularly type II diabetes. (Evans at 577-578; *see also* Wiedeman at 413; Lambeir at 210.)

123. Investigators focused on two main categories of DPP-IV inhibitors: dipeptide like inhibitors and non-peptidic inhibitors. Dipeptide-like inhibitors were well known and a well-trod area of research as of March 2004. A fresh trend of research at the time of the filing of the patent at issue here was the development and evaluation of non-peptidic inhibitors. Indeed, Merck & Co., Inc. ("Merck") were experimenting on a class of non-peptidic compounds of the general structure:



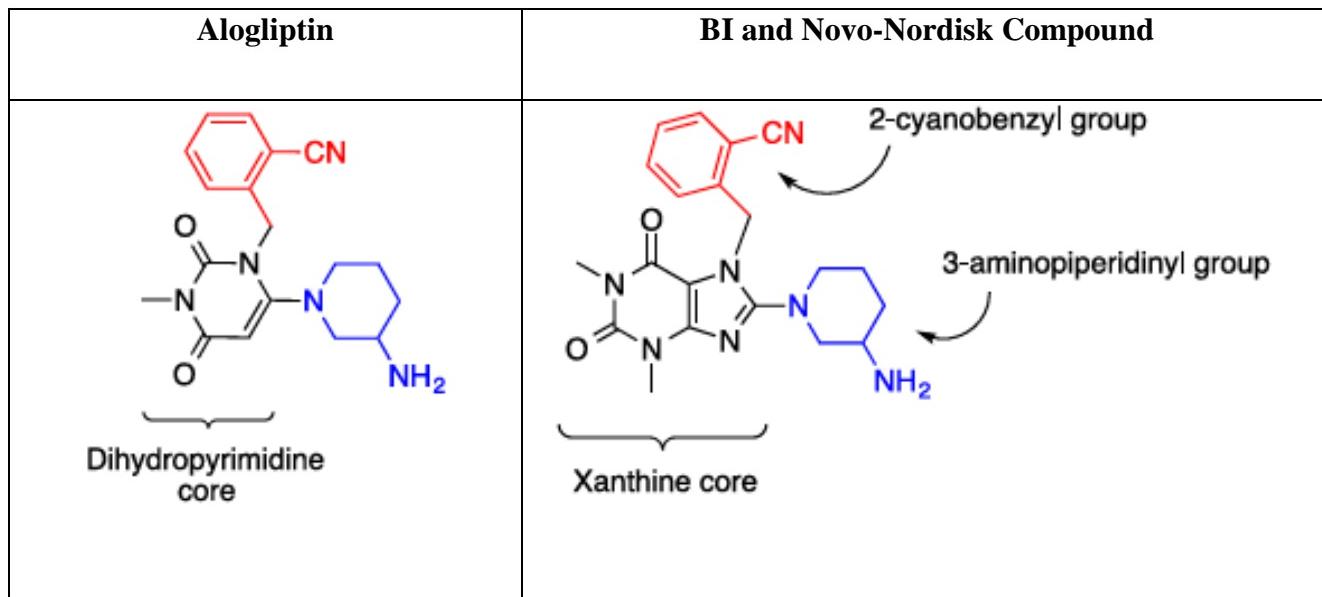
which were identified by Merck as inhibitors of the dipeptidyl peptidase-IV enzyme, and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. (U.S. Patent No. 6,699,871; WO2003/004498 A1, also assigned to Merck.)

124. According to Wiedeman, “a number of non-peptidic molecules have been disclosed as DPP-IV inhibitors. These diverse groups of molecules include core structures such as xanthines, aminomethylisoquinolones, aminomethylisoquinolines, aminolactams and sulfonyltriazoles.” (Wiedeman at 417.) Among non-peptidic DPP-IV inhibitors, compounds containing a xanthine core are one of the most promising DPP-IV inhibitors. (*Id.*) At least two competing pharmaceutical companies, Boehringer Ingelheim and Novo Nordisk were exploring such compounds.

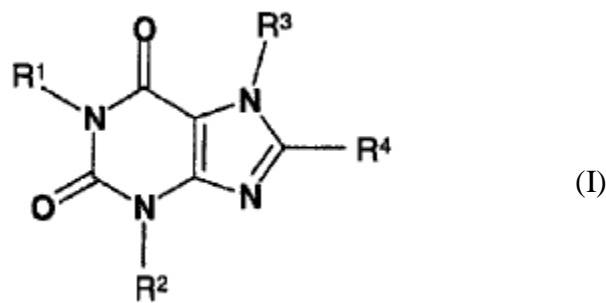
125. Boehringer Ingelheim (“BI”) disclosed a series of xanthine-core containing DPP-IV inhibitors in the WO ’420 publication, a PCT application published on September 6, 2002. I understand that the specification of the WO ’420 publication has an English language counterpart in the CA ’730 patent, which I will reference in my analysis.

126. Novo Nordisk was also investigating xanthine-core containing DPP-IV inhibitors, as indicated by the work disclosed in the WO ’496 publication, which published on January 16, 2003.

127. The research presented in the CA '730 patent and the WO '496 publication converge in that they both disclose the same compound, a xanthine-derivative remarkably structurally similar to alogliptin, as set forth below:



128. The CA '730 patent discloses DPP-IV inhibitors consisting of substituted xanthine compounds of Formula I:



129. In CA '730 patent, certain compounds of Formula I were described as particularly preferred. In those compounds:

R^1 is hydrogen, a C₁₋₄-alkyl group, among other groups;

R² is hydrogen, a C₁₋₆-alkyl group, among other groups;

R³ is a benzyl group wherein the phenyl moiety may be substituted by one or two fluorine atoms, an iodine atom, or a cyano, nitro, or amino group; and

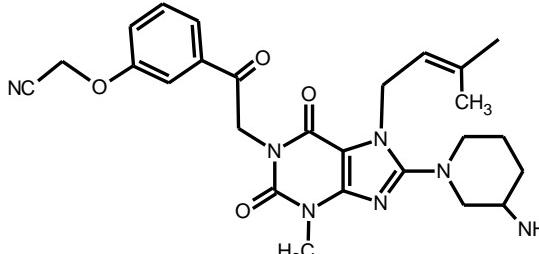
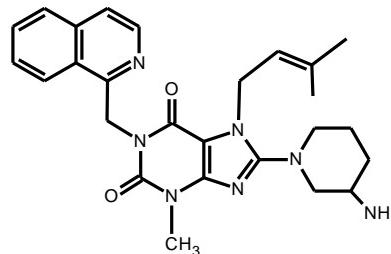
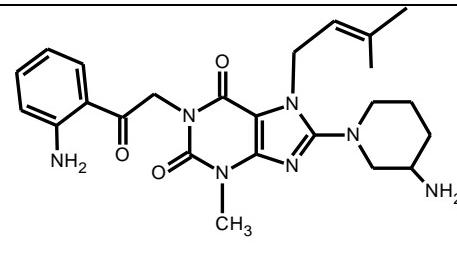
R⁴ is a piperidin-1-yl group, which is substituted in the 3-position by an amino group, wherein the piperidin-1-yl moiety may be additionally substituted by a methyl group.

See CA '730 patent, 59:12-14; 61:24-25; 62:27-28; 63:14-17.)

130. The CA '730 patent also discloses the results obtained from testing 31 compounds for their ability to inhibit DPP-IV activity. (CA '730 patent, cols. 98-100). Based on the IC₅₀ data reported in the CA '730 patent, 5 test compounds are found to exhibit DPP-IV inhibitory activity in IC₅₀ value ranging between 2 nM and 10 nM indicative of the compounds being highly potent DPP-IV inhibitors. The five compounds identified by their chemical names and respective structures are set forth in the following table together with their IC₅₀ values.

Compound	IC50 ⁴	Structure
Compound 1(121): 1,3-dimethyl-7-(2-cyano-benzyl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 197:13)	10 nM	
Compound 2(28): 1-(2-phenyl-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 204:24-25)	5 nM	

⁴ The IC₅₀ data is found in CA '730 patent at cols. 99-100.

Compound	IC50 ⁴	Structure
Compound 2(88): 1-[2-(3-cyanomethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 214:26-27)	6 nM	
Compound 2(119): 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 220:6-7)	2 nM	
Compound 2(136): 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-aminopiperidin-1-yl) xanthine (CA '730 patent, Col. 223:14-15)	3 nM	

131. The highly potent DPP-4 inhibitors set forth in the above table have common structural features. All of the five compounds contain methyl and 3-amino-piperidinyl substituents at positions 3 and 8 of the central xanthine scaffold respectively. Four of the five compounds contain a 3-methyl-2-buten-1-yl group at position 7 of the xanthine scaffold, with one compound, 1(121), containing 2-cyanobenzyl at the corresponding position of the xanthine scaffold.

132. As was already known, the CA '730 patent disclosed that the DPP-IV inhibitory activity of the compounds would make them suitable for preventing or treating diabetes mellitus,

diabetic complications, among other diseases. (*See* CA '730 patent, col. 100.)

133. Given the usefulness of DPP-IV inhibitors in the treatment of diabetes mellitus, and the interest in non-peptidic DPP-IV inhibitors containing a xanthine core (Wiedeman at 417), a person of ordinary skill in the art as of March 2004 would have been motivated to consider the five highly potent DPP-IV inhibitors of the CA '730 patent as potential lead compounds.

134. From among the five potent DPP-IV inhibitors disclosed in CA '730 patent, however, Compound 1(121) would have stood out as an interesting lead to one of ordinary skill in the art for further development of DPP-IV inhibitors for the reasons set forth below.

135. First, Novo Nordisk also identified the same compound in their development of xanthine core DPP-IV inhibitors, describing it as the first (Example) in the experimental section of their patent application. Example 1 of the WO '496 publication discloses Compound 1(121). (WO '496 publication at 37.) While the disclosure of a first example in a patent application may not necessarily suggest such compound as a "lead compound," the fact that both the CA '730 patent and WO '496 publication each independently identified the exact same compound, and further since the CA '730 patent further identified this same compound as falling in the group of the 5 best compounds based on the potent DPP-IV inhibitory activity exhibited by the compounds with IC₅₀ values ranging between 2 nM and 10 nM. This is indicative that the compound disclosed independently in the Boehringer Ingelheim and Novo Nordisk references is a highly potent DPP-IV inhibitor, and this observation provides a strong suggestion that such compounds can form a starting point of further research and development efforts. (*Compare* WO '496 at 37:16-38:10 *to* Compound 1(121) in CA '730 patent at cols. 99-100.). Indeed, finding the same highly potent DPP-IV inhibitor being independently disclosed in another

researcher's patent publication would have invoked enough interest to one of ordinary skill in the art to consider such a potent compound for further evaluation.

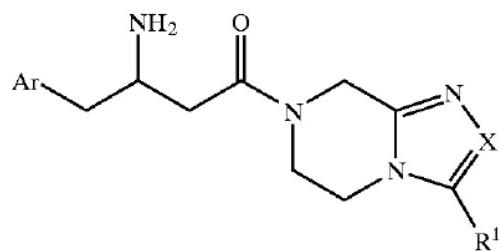
136. Second, there are several references that provide information about the structural features of a DPP-IV inhibitor, particularly the P1 and P2 groups that are crucial for the binding affinity of the DPP-IV inhibitor at the active sites of the DPP-IV enzyme. One of ordinary skill in the art would have been motivated to retain the groups that corresponds to P1 and P2 groups of Compound 1(121). These groups would have been recognized as relatively successful motifs for DPP-IV inhibitors.

137. One of ordinary skill in the art would have considered the cyano containing group of the Compound 1(121) crucial for binding to the DPP-IV enzyme active sites. Evans, for example, discloses that a cyano group residue is sufficiently electrophilic to interact with the serine hydroxyl of DPP-IV substrate. (Evans at 578.) Evans also states that the cyano group was known to not cause stability problems like other electrophilic groups such as keto and/or aldehyde groups. (Evans at 578.) A number of both peptidic and non-peptidic inhibitors utilize the cyano group. (Evans at Figures 1 (peptidic) and 6 (non-peptidic).) The WO '496 publication also contains a number of compounds with a cyano group. Further, potency of diverse cyano containing DPP-IV inhibitors would have been noticed by those of ordinary skill in the art and would have presented as a very viable option for further development. Based on the understanding of the criticality of the cyano group in certain DPP-IV inhibitors, one of ordinary skill in the art also would have rationally hypothesized that the group may interact or coordinate with the serine hydroxyl group of the DPP-IV substrate.

138. Because only Compound 1(121) contains a cyano group, one of ordinary skill in the art would have chosen it as a lead compound over the remaining highly potent DPP-IV

inhibitors disclosed in the CA '730 patent.

139. The 3-amino-piperidinyl moiety of Compound 1(121), which has a N-terminal primary amino group, also would have been retained by one of ordinary skill in the art in further development of DPP-IV inhibitors. Evans, for example, discloses that a DPP-IV inhibitor should include an N-terminal primary or secondary amine and that such a group was essential. (Evans at 577.) The majority of DPP-IV inhibitors under investigation as of March 2004 contained a primary or secondary amino group. (Wiedeman at 415 (Figure 3), 417 (Figure 7).) Indeed, Merck was experimenting on a class of non-peptidic compounds of the general structure:



which were identified by Merck as inhibitors of the dipeptidyl peptidase-IV enzyme and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. (See U.S. Patent No. 6,699,871 assigned to Merck.)

140. One of ordinary skill in the art would thus retain the cyano-containing moiety and the 3-amino-piperidinyl moiety of Compound 1(121), and would look to modify Compound 1(121) by focusing on changing the xanthine scaffold. Scaffold hopping was a known and common technique as of March 2004. In examining how to alter the xanthine scaffold, substituting a uracil scaffold would have been a very obvious choice.

141. Medicinal chemists tend to look for certain characteristics in a scaffold. Rings keep the substituents in place, but large rings can cause bulkiness. Decreasing the molecular weight of the scaffold is one common goal of lead modification. One of ordinary skill in the art thus would have substituted one ring structure for a two ring structure in Compound 1(121) to see if the compound retained its potency and determine whether the two ring structure was essential. If they had done so, they would have arrived at alogliptin.

142. In addition, xanthine is a purine base belonging to a class of nitrogen-containing bases. In considering modification of the Compound 1(121), one of ordinary skill in the art would naturally consider replacing xanthine with other nitrogen-containing bases. The usefulness of xanthine and uracil scaffolds in pharmaceutical arts was extremely well known at the time. ('051 patent at col. 4, ll. 41-46; '476 patent at col. 2, ln. 5-col. 3, ln. 6.) Because compounds with such scaffolds are similar to naturally occurring bases, they are generally considered as top choices in molecular design.

143. One of ordinary skill in the art also would have been aware that references also teach the substitution of purine bases (one of which is xanthine) with pyrimidine bases (such as uracil) in the design of therapeutically active compounds. ('051 patent at col. 4:41-46; '476 patent at col. 2:5-col. 3:6; Davies at 125, 127.) One such reference is Davies. In Davies, structural analysis showed a pattern of hydrogen bonds between the purine ring (central scaffold) of a lead compound and the enzyme at issue (cyclin-dependent kinase or CDK). In expanding from the lead compound, researchers recreated the pattern of hydrogen bonds that existed between the purine ring and CDK enzyme using a pyrimidine system. The pyrimidine compounds showed more potency than the lead purine compound.

144. The sole difference between alogliptin and Compound 1(121) is the substitution

of the xanthine core of Compound 1(121) with a uracil/pyrimidine core. Based on the knowledge of one of ordinary skill in the art in March 2004, which included knowledge of the crystal structure of the DPP-IV enzyme and the significance of utilizing the crystal structure in applying structure based drug design, this substitution would have been obvious to one of ordinary skill in the art and/or the '051 patent, the '476 patent, and Davies reference. Thus, based on the structure based drug design approach, using Compound 1(121) as a lead compound a medicinal chemist would have expected the resulting compound obtained by substituting the xanthine scaffold of the Compound 1(121) with the uracil scaffold to also have DPP-IV inhibitory activity.

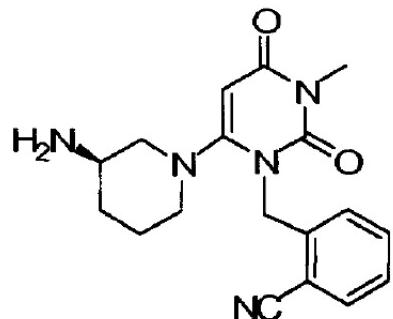
145. As set forth above, Claim 1 of the '689 patent, which covers alogliptin, is obvious based on the WO '420 publication/CA '730 patent (or WO '496, which discloses the same lead compound) in combination with what was known in the art about the structure of DPP-IV inhibitors (Evans, *see also* Engel and Artgeerts) and what was known in the art about suitable and potentially superior substitutions for xanthine scaffolds (any of the Substitution References, and the '051 patent in particular).

c. **Claims 3, 4, 9, 11, and 12 of the '689 Patent**

146. Claims 3, 4, 9, 11, and 12 of the '689 patent cover pharmaceutically acceptable salts of alogliptin, such as the benzoate salt form, and stereoisomers of alogliptin or its pharmaceutically acceptable salts:

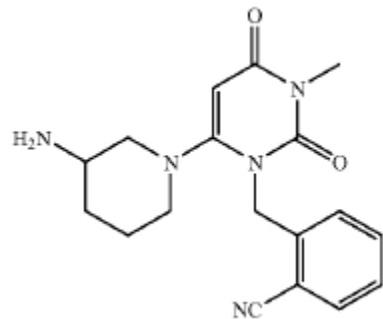
3. The compound according to claim 1, wherein the compound comprises a single stereoisomer.

4. A compound of the formula



or pharmaceutically acceptable salts thereof.

9. A compound of the formula

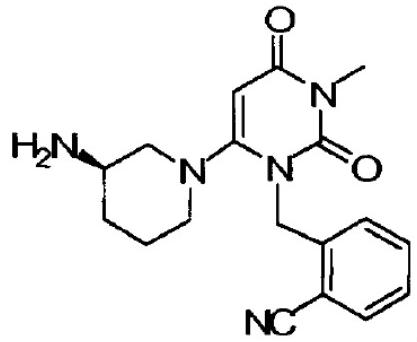


wherein the compound is present as a benzoate salt, or stereoisomers thereof.

10. The compound according to claim 9, wherein the compound is present as a mixture of stereoisomers.

11. The compound according to claim 10, wherein the compound is present as a single stereoisomer.

12. A compound of the formula



wherein the compound is present as a benzoate salt.

(a) **Stereoisomers of Alogliptin**

147. A person of ordinary skill in the art would have recognized that alogliptin is a chiral compound and thus has isomeric forms.

148. It was well known as of March 2004 to evaluate stereoisomers of pharmaceutical compounds given that the potency and toxicity of each stereoisomer may differ. (Campbell, Hutt, Crossley, and Izumi.) The stereospecificity of DPP-IV was also known. (Lambier at 220.)

149. Additionally, the CA '730 patent teaches that the compounds described in the reference (including the Compound 1(121)) can be resolved into their enantiomers and/or diastereomers and further discloses some of the known methods in the art for separation and isolation.

150. The skilled artisan would be motivated to isolate and test the characteristics of the isomers of alogliptin to optimize its properties and based on the teachings of the CA '730 patent.

(b) **Alogliptin Salts, Including Benzoate Salts**

151. By March 2004, a person of ordinary skill in the art would have been aware that certain important characteristics, such as solubility, stability, and the pharmacokinetic profile, of an active free base or acid pharmaceutical compound can be improved by making a salt from the

compound.

152. Strategies for developing and selecting suitable pharmaceutical salts were well known and in common use.

153. Drugs in the form of their benzoate salts were known for decades prior to the filing of the '689 patent. (Berge at 2, Table 1).

154. Additionally, high through-put techniques were well known as of March 2004, which enable researchers to efficiently synthesize and analyze dozens of salt forms of pharmaceutical compounds to find the most suitable salt form. This technique and its ubiquity is described in the Higgins reference, for example, at 22, 24.

155. One of ordinary skill in the art would have been motivated from the knowledge in the art and teachings such as that found in Berge and Higgins to develop pharmaceutically acceptable salts of alogliptin, including the benzoate salt form. Benzoate salts were known and have also been considered acceptable by the FDA for decades.

(c) **Obviousness of Claims 3, 4, 9, 11, and 12**

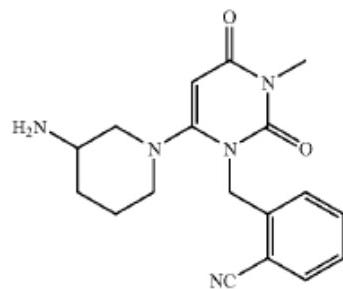
156. Section VII.C.b of my report explains why it would have been obvious to synthesize alogliptin. Section VII.C..c.(a) explains why one of ordinary skill in the art would further have isolated and studied the stereoisomers of alogliptin. Section VII.C.c explains that producing pharmaceutically acceptable salt versions of compounds, including benzoate salts, would have been a natural step as well in the optimization of alogliptin.

157. For the reasons set forth in Sections VII.C.a., VII.C.b, and VII.C.c.(a-b), Claims 3, 4, 9, 11, and 12, which claim alogliptin in various stereoisomeric forms and salts of alogliptin would have been obvious.

d. Claims 43 and 49 of the '689 Patent

158. Claims 43 and 49 of the '689 patent cover a method of treating type II diabetes using alogliptin generally (Claim 43) and the R-stereoisomer of alogliptin benzoate salt (Claim 49).

43. A method of treating type II diabetes in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of the formula



or stereoisomers or pharmaceutically acceptable salts thereof.

49. A method of treating type II diabetes in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to claim 12.

159. Both claims are obvious in light of the known utility of DPP-IV inhibitors in the treatment of type II diabetes.

160. I have already set forth my analysis of why alogliptin, its stereoisomers, and its pharmaceutically acceptable salts, including the R-stereoisomer of alogliptin benzoate salt, are obvious.

161. Multiple general references establish the utility of using DPP-IV inhibitors for the treatment of diabetes, including type II diabetes. (Evans, Wiedeman, and Lambier.) The Aertgeert reference, a crystallography study, even notes that human trials on DPP-IV inhibitors

to treat type II diabetes were ongoing as of 2003.

162. Additionally, the primary invalidity references I have used (i.e., the WO '420 publication/CA '730 patent and the WO '496 patent), which disclose the lead compound, Compound 1(121), specifically suggest the use of the compounds described in the references for the treatment of type II diabetes.

163. Based on what was known in the art and disclosed in Evans, Wiedeman, Lambier, the WO '42 publication/CA '730 patent, and the WO '496 patent, one of ordinary skill in the art would have investigated the treatment of type II diabetes with alogliptin and its improved salts and/or isolated stereoisomers -- such a treatment in fact would have been the primary goal for development of the pharmaceutical compound.

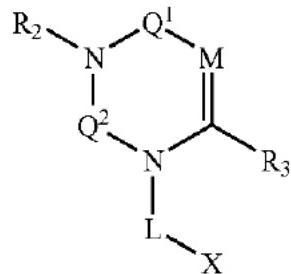
D. The '539 Patent

a. The Claims at Issue in the '539 Patent

164. I understand that Claims 2-3, 5-7, 9, 11, 15, and 18 of the '539 patent have been asserted by Takeda.

165. Claims 2-3, 5-7, 9, 11, 15, and 18 of the '539 patent all refer to Claim 1, which is not asserted. Claim 1 covers millions of nitrogen containing heterocyclic compounds, including alogliptin.

1. A compound having the formula:



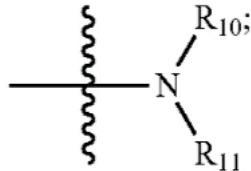
wherein:

M is CR₄;

Q¹ and Q² are each CO;

R₂ is hydrogen or selected from the group consisting of (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, (C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₁₋₅)alkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl(C₁₋₅)alkyl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino (C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxyl, alkoxy, aryloxy, heteroaryloxy, and carbonyl group, each substituted or unsubstituted;

R₃ has the formula



R₁₀ and R₁₁ are each independently selected from the group consisting of hydrogen, perhalo(C₁₋₁₀)alkyl, (C₁₋₁₀)alkyl, (C₃₋₁₂)cycloalkyl, hetero(C₃₋₁₂)cycloalkyl, aryl(C₁₋₁₀)alkyl, heteroaryl(C₁₋₅)alkyl, (C₉₋₁₂)bicycloaryl, hetero(C₄₋₁₂)bicycloaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, and carbonyl group, each substituted or unsubstituted, or R₁₀ and R₁₁ are taken together to form a 4,5,6, or 7 membered ring,

each substituted or unsubstituted;

R₄ is hydrogen or selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino (C₁₋₃)alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, and carbonyl group, each substituted or unsubstituted;

-L-X taken together is selected from the group consisting of -(CH₂)-(2-cyano)phenyl; -(CH₂)-(3-cyano)phenyl; -(CH₂)-(2-hydroxy)phenyl; -(CH₂)-(3-hydroxy)phenyl; -(CH₂)-(2-alkenyl)phenyl; -(CH₂)-(3-alkenyl)phenyl; -(CH₂)-(2-alkynyl)phenyl; -(CH₂)-(3-alkynyl)phenyl; -(CH₂)-(2-methoxyl)phenyl; -(CH₂)-(3-methoxyl)phenyl; -(CH₂)-(2-nitro)phenyl; -(CH₂)-(3-nitro)phenyl; -(CH₂)-(2-carboxy)phenyl; -(CH₂)-(3-carboxy)phenyl; -(CH₂)-(2-carboxamido)phenyl; -(CH₂)-(3-carboxamido)phenyl; -(CH₂)-(2-sulfonamido)phenyl; -(CH₂)-(3-sulfonamido)phenyl; -(CH₂)-(2-tetrazolyl)phenyl; -(CH₂)-(3-tetrazolyl)phenyl; -(CH₂)-(2-aminomethyl)phenyl; -(CH₂)-(3-aminomethyl)phenyl; -(CH₂)-(2-hydroxymethyl)phenyl; -(CH₂)-(3-hydroxymethyl)phenyl; -(CH₂)-(2-phenyl)phenyl; -(CH₂)-(3-phenyl)phenyl; -(CH₂)-(2-halo)phenyl; -(CH₂)-(3-halo)phenyl; -(CH₂)-(2-CONH₂)phenyl; -(CH₂)-(3-CONH₂)phenyl; -(CH₂)-(2-CONH(C₁₋₇)alkyl)phenyl; -(CH₂)-(2-CO₂(C₁₋₇)alkyl)phenyl; -(CH₂)-(3-CO₂(C₁₋₇)alkyl)phenyl; -(CH₂)-(2-NH₂)phenyl; -(CH₂)-(3-NH₂)phenyl; -(CH₂)-(2-(C₃₋₇)alkyl)phenyl; -(CH₂)-(3-(C₃₋₇)alkyl)phenyl; -(CH₂)-(2-(C₃₋₇)cycloalkyl)phenyl; -(CH₂)-(3-(C₃₋₇)cycloalkyl)phenyl; -(CH₂)-(2-aryl)phenyl; -(CH₂)-(3-aryl)phenyl; -(CH₂)-(2-heteroaryl)phenyl; -(CH₂)-(3-heteroaryl)phenyl; -(CH₂)-2-bromo-5-fluoro phenyl; -(CH₂)-2-chloro-5-fluoro phenyl; -(CH₂)-2-cyano-5-fluoro phenyl; -(CH₂)-2,5-dichloro phenyl; -(CH₂)-2,5-difluoro

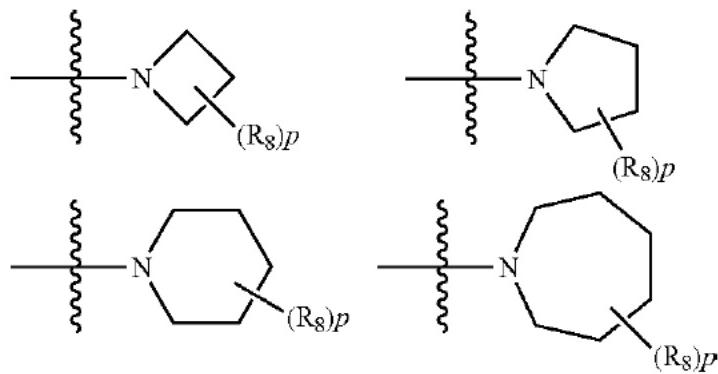
phenyl; $-(\text{CH}_2)-2,5$ -dibromo phenyl; $-(\text{CH}_2)-2$ -bromo-3,5-difluoro phenyl; $-(\text{CH}_2)-2$ -chloro-3,5-difluoro phenyl; $-(\text{CH}_2)-2,3,5$ -trifluoro phenyl; $-(\text{CH}_2)-2,3,5,6$ -tetrafluorophenyl; $-(\text{CH}_2)-2$ -bromo-3,5,6-trifluoro phenyl; $-(\text{CH}_2)-2$ -chloro-3,5, 6-trifluoro phenyl; $-(\text{CH}_2)-2$ -cyano-3,5-difluoro phenyl; $-(\text{CH}_2)-2$ -cyano-3,5,6-trifluoro phenyl; $-(\text{CH}_2)-(2$ -heterocycloalkyl)phenyl; and $-(\text{CH}_2)-(3$ -heterocycloalkyl)phenyl, each substituted or unsubstituted;

166. Claims 2-3, 5-7, 9, 11, 15, and 18 of the '539 patent are genus claims that cover multiple species of nitrogen containing heterocyclic compounds.

2. The compound according to claim 1, wherein R_3 is a substituted or unsubstituted 3, 4, 5, 6, or 7 membered ring.

3. The compound according to claim 1, wherein R_3 is a substituted or unsubstituted 4, 5, 6, or 7 membered heterocycloalkyl.

5. The compound according to claim 1, wherein R_3 is selected from the group consisting of



wherein p is 0-12 and each R_8 is independently selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3 , cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl,

alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, and carbonyl group, each substituted or unsubstituted.

6. The compound according to claim 5, wherein at least one R₈ comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein.

7. The compound of claim 6, wherein the basic nitrogen atom forms part of a primary, secondary or tertiary amine.

9. The compound according to claim 5, wherein at least one R₈ is a primary, secondary or tertiary amine.

11. The compound according to claim 5, wherein at least one R₈ is selected from the group consisting of -NH₂, -NH(C₁₋₅ alkyl), -N(C₁₋₅ alkyl)₂, piperazine, imidazole, and pyridine.

15. The compound of claim 14,⁵ wherein the basic nitrogen of R₃ is separated from the ring atom to which R₃ is attached by between 1-5 atoms.

18. The compound according to claim 1, wherein M is CH; R₇ is a substituted or unsubstituted (C₁₋₁₀)alkyl; and R₃ is selected from the group consisting of 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 3-aminoazetidin-1-yl, 3-amino-3-methyl piperidin-1-yl, 3-aminohexahydroazepin-1-yl, piperazin-1-yl, homopiperazin-1-yl, R-3 aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, and 3-aminopyrrolidin-1-yl, each substituted or unsubstituted.

167. Alogliptin is a species falling within each of the asserted claims of the '539

⁵ Claim 14 covers "the compound according to claim 1, wherein R₃ comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein."

patent.

168. I have been instructed to assume that, for purposes of invalidity, the priority date for the '539 patent is March 15, 2004. I rely on the same references as set forth in Section VII.B. above, all of which are dated before March 15, 2004.

b. The Claims at Issue in the '539 Patent Are Obvious

169. I have provided earlier my opinion that alogliptin would have been obvious in view of the prior art and knowledge of one of ordinary skill in the art, as set forth in Section VII.C. above. I incorporate by reference that argument here.

170. It is my understanding that the prior disclosure of a species will anticipate a genus.

171. Because alogliptin is obvious, the genus claims covering alogliptin, Claims 2-3, 5-7, 9, 11, 15, and 18 of the '539 patent, would also have been obvious.

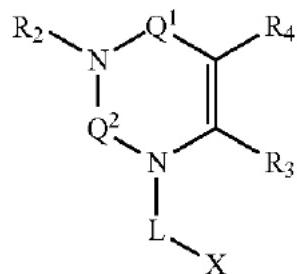
E. The '663 Patent

a. The Claims at Issue in the '663 Patent

172. I understand that Claims 1, 4, 6-8, 10, 12, 14-17, 19-21, 27, and 29 of the '663 patent have been asserted by Takeda.

173. Claim 1 of the '663 patent covers a method of treating type II diabetes by administration of dipeptidyl peptidase inhibitors that are nitrogen containing heterocyclic compounds represented by a general formula. This general formula covers millions of compounds, including alogliptin.

1. A method of treating type II diabetes in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a compound having the formula:

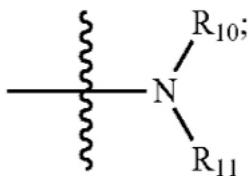


wherein:

Q^1 and Q^2 are each CO;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxyl, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group , each substituted or unsubstituted;

R_3 comprises the formula



R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, perhalo(C_{1-10})alkyl, (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, or R_{10} and R_{11} are taken together to form a 4,5,6, or 7 membered ring, each substituted or unsubstituted;

R_4 is hydrogen or selected from the group consisting of halo,

perhalo(C₁₋₁₀)alkyl, amino, cyano, thio, (C₁₋₁₀)alkyl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, carbonyl (C₁₋₃)alkyl, thiocarbonyl (C₁₋₃)alkyl, sulfonyl (C₁₋₃)alkyl, sulfinyl(C₁₋₃)alkyl, imino (C₁₋₃)alkyl, hydroxyl, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

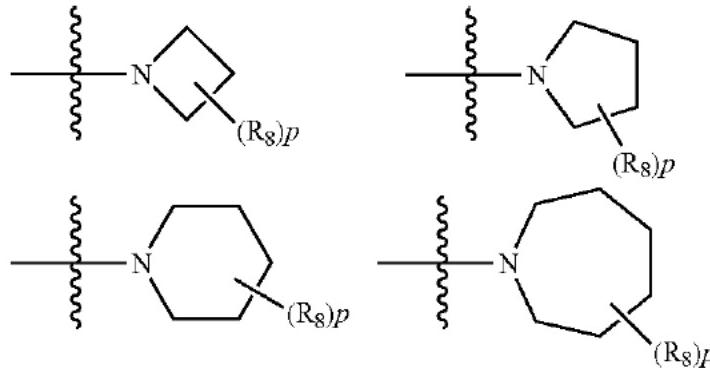
-L-X taken together is selected from the group consisting of –(CH₂)-(2-cyano)phenyl; –(CH₂)-(3-cyano)phenyl; –(CH₂)-(2-hydroxy)phenyl; –(CH₂)-(3-hydroxy)phenyl; –(CH₂)-(2-alkenyl)phenyl; –(CH₂)-(3-alkenyl)phenyl; –(CH₂)-(2-alkynyl)phenyl; –(CH₂)-(3-alkynyl)phenyl; –(CH₂)-(2-methoxyl)phenyl; –(CH₂)-(3-methoxyl)phenyl; –(CH₂)-(2-nitro)phenyl; –(CH₂)-(3-nitro)phenyl; –(CH₂)-(2-carboxy)phenyl; –(CH₂)-(3-carboxy)phenyl; –(CH₂)-(2-carboxamido)phenyl; –(CH₂)-(3-carboxamido)phenyl; –(CH₂)-(2-sulfonamido)phenyl; –(CH₂)-(3-sulfonamido)phenyl; –(CH₂)-(2-tetrazolyl)phenyl; –(CH₂)-(3-tetrazolyl)phenyl; –(CH₂)-(2-aminomethyl)phenyl; –(CH₂)-(3-aminomethyl)phenyl; –(CH₂)-(2-hydroxymethyl)phenyl; –(CH₂)-(3-hydroxymethyl)phenyl; –(CH₂)-(2-phenyl)phenyl; –(CH₂)-(3-phenyl)phenyl; –(CH₂)-(2-halo)phenyl; –(CH₂)-(3-halo)phenyl; –(CH₂)-(2-CONH₂)phenyl; –(CH₂)-(3-CONH₂)phenyl; –(CH₂)-(2-CONH(C₁₋₇) alkyl)phenyl; –(CH₂)-(3-CONH(C₁₋₇)alkyl)phenyl; –(CH₂)-(2-CO₂(C₁₋₇)alkyl)phenyl; –(CH₂)-(3-CO₂(C₁₋₇)alkyl)phenyl; –(CH₂)-(2-NH₂)phenyl; –(CH₂)-(3-NH₂)phenyl; –(CH₂)-(2-(C₃₋₇)alkyl)phenyl; –(CH₂)-(3-(C₃₋₇)alkyl)phenyl; –(CH₂)-(2-(C₃₋₇)cycloalkyl)phenyl; –(CH₂)-(3-(C₃₋₇)cycloalkyl)phenyl; –(CH₂)-(2-aryl)phenyl; –(CH₂)-(3-aryl)phenyl; –(CH₂)-(2-heteroaryl)phenyl; –(CH₂)-(3-heteroaryl)phenyl; –(CH₂)-2-bromo-5-fluoro phenyl; –(CH₂)-2-chloro-5-fluoro phenyl; –(CH₂)-2-cyano-5-fluoro phenyl; –(CH₂)-2,5-dichloro phenyl; –(CH₂)-2,5-difluoro phenyl; –(CH₂)-2,5-dibromo phenyl; –(CH₂)-2-bromo-3,5-difluoro phenyl; –(CH₂)-2-chloro-3,5-difluoro phenyl; –(CH₂)-2,3,5-trifluoro phenyl; –(CH₂)-2,3,5,6-tetrafluorophenyl; –(CH₂)-2-bromo-3,5,6-trifluoro phenyl; –(CH₂)-2-chloro-3,5,6-trifluoro phenyl; –(CH₂)-2-cyano-3,5-difluoro phenyl; –(CH₂)-2-cyano-3,5,6-trifluoro phenyl; –(CH₂)-(2-heterocycloalkyl)phenyl; and –(CH₂)-(3-heterocycloalkyl)phenyl, each substituted or unsubstituted.

174. Claims 4, 6-8, 10, 12, 14-17, 19-21, 27, and 29 claim the treatment of type II

diabetes with compounds that fall in broad genuses within the general formula of Claim 1:

4. The method according to claim 1, wherein R₃ is a substituted or unsubstituted 4, 5, 6, or 7 membered heterocycloalkyl.

6. The method according to claim 1, wherein R₃ is selected from the group consisting of



wherein p is 0-12 and each R₈ is independently selected from the group consisting of halo, perhalo(C₁₋₁₀)alkyl, CF₃, cyano, nitro, hydroxy, alkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, alkoxy, carbonyl group, imino group, sulfonyl group, and sulfinyl group, each substituted or unsubstituted.

7. The method according to claim 6, wherein at least one R₈ comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein.

8. The method according to claim 7, wherein the basic nitrogen atom forms part of a primary, secondary or tertiary amine.

10. The method according to claim 6, wherein at least one R₈ is a primary, secondary or tertiary amine.

12. The method according to claim 6, wherein at least one

R₈ is selected from the group consisting of –NH₂, –NH(C₁₋₅ alkyl), –N(C₁₋₅ alkyl)₂, piperazine, imidazole, and pyridine.

14. The method according to claim 1, wherein R₃ is substituted such that R₃ comprises a substituent selected from the group consisting of a primary, secondary or tertiary amine, a heterocycloalkyl comprising a nitrogen ring atom, and a heteroaryl comprising a nitrogen ring atom.

15. The method according to claim 1, wherein R₃ comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein.

16. The method according to claim 15, wherein the basic nitrogen of R₃ is separated from the ring atom to which R₃ is attached by between 1-5 atoms.

17. The method according to claim 15, wherein the basic nitrogen atom forms part of a primary, secondary or tertiary amine.

18. The method according to claim 15, wherein the basic nitrogen atom is a nitrogen ring atom of a heterocycloalkyl or a heteroaryl.

19. The method according to claim 1, wherein R₃ is selected from the group consisting of 3-amino-piperidinyl-1-yl, 3-aminomethyl-pyrrolidin-1-yl, 3-aminoazetidin-1-yl, 3-amino-3-methylpiperidin-1-yl, 3-aminohexahydroazepin-1-yl, piperazin-1-yl, homopiperazin-1-yl, R-3 aminopiperidin-1-yl, R-3-amino-3-methylpiperidin-1-yl, and 3-aminopyrrolidin-1-yl, each substituted or unsubstituted.

20. The method according to claim 1, wherein R₂ is a substituted or unsubstituted (C₁₋₁₀)alkyl.

21. The method according to claim 1, wherein R₂ is a substituted or unsubstituted (C₁₋₄)alkyl.

27. The method according to claim 1, wherein the compound is in the form of a pharmaceutically acceptable salt.

29. The method according to claim 1, wherein the compound comprises a single stereoisomer.

175. Alogliptin is a species falling within each of the asserted claims of the '663 patent.

176. I have been instructed to assume that, for purposes of invalidity, the priority date for the '663 patent is March 15, 2004. I rely on the same references as set forth in Section VII.B. above, all of which are dated before March 15, 2004.

b. **The Claims at Issue in the '663 Patent Are Obvious**

177. I have provided earlier my opinion that alogliptin would have been obvious to one of ordinary skill in the art in view of the prior art and knowledge of one of ordinary skill in the art, as set forth in Sections VII.A. and VII.B. above. I have also provided my opinion that isolation of a single stereoisomer of alogliptin, as well as the development of pharmaceutically acceptable salts of alogliptin, including the benzoate salt, would have been obvious, as set forth in Section VII.C. I incorporate by reference these arguments here.

178. It is my understanding that the prior disclosure of a species will anticipate a genus.

179. Because the use of alogliptin, stereoisomers of alogliptin, and pharmaceutically acceptable salts of alogliptin for the treatment of type II diabetes is obvious, the genus claims that incorporate such compounds and salts, Claims 1, 4, 6-8, 10, 12, 14-21, 27, and 29 of the '663 patent, would also have been obvious.

VIII. SECONDARY CONSIDERATIONS

180. At this time, I am not aware of any secondary considerations that would change my opinions that the asserted claims are invalid as obvious as set forth above. I understand from counsel that I will have an opportunity to address any secondary considerations that Plaintiffs raises in my rebuttal report. I also understand from counsel that Plaintiffs have not asserted commercial success as evidence of a secondary consideration of non-obviousness.

IX. SUPPLEMENTATION AND REBUTTAL

181. I reserve the right to revise or supplement my opinions set forth in this report, for example, based on information submitted by Plaintiffs' experts, any additional references, documents, or testimony that I receive, information provided to me through the discovery process, or any other supplemental information I am made aware of as part of this litigation process. My opinions are based on the information I have relied upon in Exhibit A and my professional experience and education.

182. If asked, I will testify at a trial in this case based on the opinions of this report and any rebuttal and supplemental reports. At trial, I may explain concepts and terminology from my report to make the material as accessible as possible for the judge. I reserve the right to use demonstrative exhibits to assist in explaining the technology and the opinions I have reached. I also reserve the right to comment on or testify in response to trial testimony from any other witness, including Plaintiffs' witnesses and any experts retained by Plaintiffs.

X. CONCLUSION

183. For the reasons explained in this report, it is my opinion that one of ordinary skill in the art in March 2004 would have considered the asserted claims invalid as obvious over the combinations of references set forth above.

Signed this 14th day of June, 2019.



Dana Ferraris, Ph.D., M.B.A.

EXHIBIT A**MATERIALS CONSIDERED**

Description	Document Production Range
U.S. Patent No. 7,807,689	
U.S. Patent No. 8,288,539	
U.S. Patent No. 8,176,663	
File History of Patent No. 7,807,689 & References	
File History of Patent No. 8,288,539 & References	
File History of Patent No. 8,176,663 & References	
U.S. Patent No. 5,142,051 to Holy et al., <i>N-Phosphonylmethoxyalkyl Derivatives of Pyrimidine and Purine Bases and a Therapeutical Composition Therefrom with Antiviral Activity</i> , issued Aug. 25, 1992	IndAlo0000990- IndAlo0000996
U.S. Patent No. 5,780,476 to Underiner et al., <i>Hydroxyl-Containing Xanthine Compounds</i> , issued July 14, 1998	IndAlo0000997- IndAlo0001036
U.S. Patent No. 6,699,871 to Edmondson et al., <i>Beta-Amino Heterocyclic Dipeptidyl Peptidase Inhibitors for the Treatment or Prevention of Diabetes</i> , issued March 2, 2004	IndAlo0079268- IndAlo0079290
Canadian Patent No. CA 2 435 730, <i>Xanthine Derivatives, The Preparation Thereof and Their Use As Pharmaceutical Compositions</i> , published Jan. 16, 2003	IndAlo0000374- IndAlo0000737
Canadian Patent No. CA 2 496 249 to Himmelsbach et al., <i>8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments</i> , published on March 4, 2004	IndAlo0045116- IndAlo0045335
International Publication WO 03/004496 to Kanstrup et al., <i>DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes</i> , published Jan. 16, 2003	IndAlo0000738- IndAlo0000839
International Publication WO 2003/004498 to Edmonson, <i>Beta-amino Tetrahydroimidazo (1, 2-a) Pyrazines And Tetrahydrotriazolo (4, 3-a) Pyrazines As Dipeptidyl</i>	IndAlo0079291- IndAlo0079359

<i>Peptidase Inhibitors For The Treatment Or Prevention Of Diabetes</i> , published Jan. 16, 2003	
International Publication WO 2002/068420 A1, <i>Xanthine Derivatives, Production and Use Thereof As Medicament</i> , filed Feb. 21, 2002 and published Sept. 6, 2002	IndAlo0000001- IndAlo000373
Aertgeerts, K., et al., <i>Crystal structure of human dipeptidyl peptidase IV in complex with a decapeptide reveals details on substrate specificity and tetrahedral intermediate formulation</i> , 13(2) Protein Sci. 412-421 (Feb. 2004)	IndAlo0000952- IndAlo0000963
Ahrén, B. et al., <i>Inhibition Of Dipeptidyl Peptidase IV Improves Metabolic Control Over A 4-Week Study Period In Type 2 Diabetes</i> , 25(5) Diabetes Care 869–875 (May 2002)	IndAlo0079111- IndAlo0079117
Anderson, A., <i>The Process of Structure-Based Drug Design</i> , 10(9) Chem. & Bio. 787-797 (Sept. 2003)	IndAlo0000966- IndAlo0000976
Berge, S., et al., <i>Pharmaceutical Salts</i> , 66(1) J. Pharm. Sci., 1-19 (Jan. 1977)	IndAlo0044978- IndAlo0044996
Böhm, H. et al., <i>Scaffold Hopping</i> , 1(3) Drug Discovery Today: Technologies 217-223 (Dec. 2004)	IndAlo0079118- IndAlo0079125
Campbell, D.B., <i>Stereoselectivity in Clinical Pharmacokinetics and Drug Development</i> , 15(2) Euro. J. Drug Metabolism & Pharmacokinetics, 109-125 (April 1990)	IndAlo0045336- IndAlo0045354
Crossley, R., <i>Chirality and the Biological Activity of Drugs</i> , CRC Press (1995)	IndAlo0045355- IndAlo0045378
Davies, T.G., et al., <i>Structure-based design of cyclin-dependent kinase inhibitors</i> , 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002)	IndAlo0001037- IndAlo0001045
Engel, M., et al., <i>The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism</i> , 100(9) PNAS 5063-068 (Apr. 29, 2003)	IndAlo0000946- IndAlo0000951
Evans, D., <i>Dipeptidyl Peptidase IV Inhibitors</i> , 5(6) IDrugs 577-585 (Jun. 2002)	IndAlo0000840- IndAlo0000848

Genuth S., et al., <i>Follow-up Report on the Diagnosis of Diabetes Mellitus</i> , 26(11) Diabetes Care 3160–167 (Nov. 2003)	IndAlo0079126- IndAlo0079133
Gutzwiller, J. et al., <i>Glucagon-Like Peptide-1 Promotes Satiety And Reduces Food Intake In Patients With Diabetes Mellitus Type 2</i> , 276(5) Am. J. Physiol. R1541–4 (May 1999)	IndAlo0079134- IndAlo0079137
Higgins, J., <i>Pharmaceutical Preformulation</i> , Today's Chemist at Work 22-26 (July 2003)	IndAlo0045596- IndAlo0045599
Holst, J., et al., <i>Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes</i> , 47(11) Diabetes 1663–670 (Nov. 1998)	IndAlo0079138- IndAlo0079145
Hundal, R., <i>Metformin: New Understandings, New Uses</i> , 63(18) Drugs 1879–894 (2003)	IndAlo0079146- IndAlo0079161
Hutt, A.J., <i>The Development of Single-Isomer Molecules: Why and How</i> , 7(4 supp. 1) CNS Spect. 14-22 (2002)	IndAlo0045600- IndAlo0045608
Inzucchi, S., <i>Oral Antihyperglycemic Therapy For Type 2 Diabetes: Scientific Review</i> , 287(3) JAMA. 360–372 (Jan. 16, 2002)	IndAlo0079162- IndAlo0079174
Izumi, T., et al., <i>Pharmacokinetics of Troglitazone, an Antidiabetic Agent: Prediction of In Vivo Stereoselective Sulfation and Glucuronidation from In Vitro Data</i> , 280(3) J. Pharm. & Experimental Therapeutics, 1392-1400 (March 1997)	IndAlo0045609- IndAlo0045617
Lambeir, A., <i>Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV</i> , 40(3) Crit. Rev. Clin. Lab. Sci. 209-294, 216 (Jun. 2003)	IndAlo0000858- IndAlo0000945
Manual of Patent Examining Procedure, Ninth Ed., Last Revised January 2018, Section 2143	
McGaughey, G., et al., <i>pi-Stacking Interactions. Alive and Well in Proteins</i> , 273(25) J. Bio. Chem. 15458–463 (Jun. 1998)	IndAlo0079175- IndAlo0079181

Mentlein, R., <i>Dipeptidyl-Peptidase IV (CD26)--Role In The Inactivation Of Regulatory Peptides</i> . 85(1) Regul Pept. 9–24 (Nov. 30, 1999)	IndAlo0079182- IndAlo0079197
Rasmussen H., et al., <i>Crystal Structure of Human Dipeptidyl Peptidase IV/CD26 in Complex with a Substrate Analog</i> , 10(1) Nat. Struct. Biol. 19-25 (Jan. 2003)	IndAlo0079198- IndAlo0079206
<i>Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus</i> , 20(7) Diabetes Care 1183–1197 (Jul. 1997)	IndAlo0079207- IndAlo0079222
Setter, S. et al., <i>Metformin Hydrochloride In The Treatment Of Type 2 Diabetes Mellitus: A Clinical Review With A Focus On Dual Therapy</i> , 25(12) Clin Ther. 2991–3026 (Dec. 2003)	IndAlo0079223- IndAlo0079259
Stratton, I., <i>Association Of Glycaemia With Macrovascular And Microvascular Complications Of Type 2 Diabetes (UKPDS 35): Prospective Observational Study</i> ,” 321(7258) Br. Med. J. 405-412 (Aug. 12, 2000)	IndAlo0079260- IndAlo0079267
Wiedeman, P. et al., <i>Dipeptidyl Peptidase IV Inhibitors For The Treatment Of Impaired Glucose Tolerance And Type 2 Diabetes</i> , 4(4) Current Op. Investigational Drugs 412-420 (Apr. 2003)	IndAlo0000849- IndAlo0000857

EXHIBIT B

CURRICULUM VITAE OF DR. DANA FERRARIS

Dana Ferraris, PhD, MBA

Department of Chemistry

McDaniel College

2 College Hill

Westminster, MD 21157

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Education

Johns Hopkins University, Carey Business School	2004-2009
<i>Masters of Business Administration</i>	
Johns Hopkins University	1994-2000
<i>Ph. D. in Organic Chemistry, Advisor: Dr. Thomas Lectka</i>	
Lafayette College	1990-1994
<i>Bachelor of Arts in Biochemistry</i>	

Professional Experience

McDaniel College

<i>Visiting Assistant Professor of Chemistry</i>	September 2015- December 2016
<i>Associate Professor of Chemistry</i>	December 2016-present
<i>Chair, Department of Chemistry</i>	November 2017-present

- Designed a Health Science Major and Biomedical Science Major and obtained approval from Academic Affairs and Board of Trustees
- Initiated the creation of a STEM learning center for tutoring that serves the growing numbers of students who are taking STEM courses at the college by helping to improve general study habits and quantitative reasoning skills
- Prepared lecture materials, homework assignments and exams for Organic Chemistry 1 & 2, Organic Chemistry Laboratory 1 & 2, Medicinal Chemistry, Chemical Literature, Senior Seminar and Independent Research
- Utilized online web learning WILEYPLUS for practice problems, skill building and homework assignments and exams
- Utilized and facilitated group oriented problem solving sessions during class
- Designed organic chemistry laboratory experiments to coincide with classwork
- Mentored undergraduate students towards completion of two medicinal chemistry projects: 1) *Design and synthesis of Inhibitors of PARP-14 for Cancer therapy*; 2)

Design, synthesis, and anti-neoplastic evaluation of dimeric amino-naphthoquinones against acute myeloid leukemia (AML)

- Established research collaborations with ten groups around the globe including University of Maryland Cancer Center (Dr. Ashkan Emadi and Dr. Rena Lapidus), Karolinska Institutet in Sweden (Dr. Herwig Schüler), University of Iowa Medicine (Dr. Anthony Fehr); JHU School of Public Health (Dr. Anthony Leung); Centre National de la Recherche scientifique, France (Dr. Katia Zanier), University of Turku Institute of Biomedicine, Finland (Dr. Arto Pulliainen), Harvard Medical School (Dr. David Sinclair), University of Manchester, England (Dr. Adam Hurlstone), University of Debrecen, Hungary (Dr. Laszlo Virag), Pennsylvania State University (Dr. Claudia Nicolae)

Stevenson University- Visiting Assistant Professor of Chemistry

2014-2015

- Prepared lecture materials, homework assignments and exams for General Chemistry, Organic Chemistry, Organic Chemistry Laboratory and Independent Research (CHEM 365)
 - Utilized online web learning by Cengage Learning Solutions and WILEYPLUS for practice problems, skill building and homework assignments
 - Utilized and facilitated group oriented problem solving sessions
 - Demonstrated and instructed students on the classical techniques necessary for an organic chemistry laboratory, namely reaction set-up, reaction workup, purification, and characterization of organic compounds
 - Mentored two undergraduate students towards completion of a medicinal chemistry project: *Design and synthesis of Inhibitors for mono-ADPribosyl transferases*

**Johns Hopkins University Brain Science Institute
Neurotranslational Drug Discovery Program**
Principal Scientist

2009-2014

- **Managing Collaborations** with pharmaceutical companies, academic labs and contract service providers:
 - Reviewed internal grants to fund JHU academic labs with the goal of translating exploratory research into validated drug discovery projects
 - Evaluated over 60 projects at JHU and initiated collaborations with 6 academic groups for translational research
 - Worked with a team of scientists and business development personnel to establish a high throughput screening (HTS) collaboration between JHU and Eisai Pharmaceuticals
 - Regularly interact with Eisai to advance and validate targets for HTS
 - Crafted research budget and plan to obtain funding from corporate sources to advance a drug discovery project from validation through lead optimization
 - Managed interactions with contract research organizations to obtain over 20 probe compounds to advance exploratory projects from JHU academic labs

- **Leading Translational Drug Discovery Research Teams:**
 - Managed medicinal chemistry teams to design and synthesize inhibitors from lead optimization through preclinical characterization for several drug discovery projects
 - Drug discovery projects include: protein-protein interactions (Glutaminase), metalloproteases (GCPII), Kinases (DLK), oxidases (DAAO) and GPCRs (SNSR4)
 - Regularly interacted across disciplines with biologists, computational chemists, pharmacologists, ADME experts, patent attorneys and business development
- **Teaching Drug Discovery**
 - Presented graduate-level drug discovery lectures for multiple courses: “Case Studies in Drug Discovery”, “Introduction to Drug Discovery” and “Neurotherapeutics”

Eisai Pharmaceuticals **2008-2009**

Principal Scientist

- **Managed relationships with Eisai process development group** and with contract research organizations to optimize process route to clinical candidate MGI-25208 (cytidine deaminase inhibitor, oncology, preclinical)
- **Assembled transition packages** for integration of cytidine deaminase and PARP programs into Eisai’s R&D pipeline in Japan and US

MGI Pharma **2004-2007**

Senior Scientist/Principal Scientist

- **Analyzed new product opportunities** by interacting with an interdisciplinary team of scientists and commercial professionals in the acquisition of assets from US and European academic and corporate sources to support sustained growth of the MGI R&D pipeline; completed one acquisition (AKR-501)
- **Managed medicinal chemistry team** from lead optimization through pre-clinical development for rare disease: discovered cytidine deaminase inhibitor (MGI-25208, ASTX727) as a co-administered therapy for myelodysplastic syndrome
- **Assisted development teams** in assembling the IND for PARP-1 inhibitor MGI-21016 (E7016, oncology, Phase 3)

Guilford Pharmaceuticals **1999-2004**

Scientist/Senior Scientist

- **Established and managed medicinal chemistry teams** for several drug discovery projects including PARP-1, DPP-IV, Glutaminase and D-Amino Acid Oxidase
- **Communicated project data across disciplines** with biologists, biochemists, ADME specialists and patent attorneys
- **Wrote research plans** for two funded SBIR grants

Awards and Honors

- Ira G. Zepp Teaching Enhancement Grant, **2019**
 - Award presented and \$10,000 in funding given for proposal of the design of a STEM learning center
- Charles A. Boehlke Jr. Engaged Faculty Fellows Award, **2018-present**
 - Award presented to five faculty members who have demonstrated exceptional mentoring
- Faculty Scholarly Publications Award, **2017-2018**
- Nora Roberts Award for Community Outreach, **2016-2017**
 - Established a High School Science Outreach Program
- Ernest M. Marks Award for excellence in chemical research, Johns Hopkins University, **1998**
- William Hart Award for excellence in undergraduate chemistry research, Lafayette College, **1994**
- Aaron O. Hoff Leadership Award, Lafayette College, **1994**
- Presidents Cup for outstanding community service and philanthropy, Lafayette College, **1993**

Professional Affiliations

- **American Chemical Society**
 - *President, Maryland Section of ACS* **2019-present**

Organize regular events and programming for the local section, responsible for communication and dissemination of information, responsible for keeping a balanced budget of ~\$50K per year, reporting activities to the national ACS
 - *Councilor, Maryland section* **2011-present**
 - Elected official of the American Chemical Society, representative of the local section, responsible for voting on issues important to the ACS, primary liaison responsible for dissemination of information and services from the national offices to the local section
 - *Member, Committee on Economic and Professional Affairs (CEPA)* **2012-2018**
 - Responsible for managing national career events, hiring career counselors, crafting salary surveys, monitoring and improving career services and researching current macroeconomic trends for employment of chemists
 - *Associate Member, Budget and Finance Committee* **2019-present**
 - Responsible for receiving and reviewing requests for funding of new and unbudgeted items, recommending approval or disapproval of the requests, and suggesting and identifying sources of funds if the request is to be

- approved; responsible for recommending to the Board of Directors and Council, as appropriate, an order of priorities, including termination of programs, based upon determination of costs and effectiveness
- *Remsen Award Chairman* **2010-present**
 - Responsible for soliciting nominations and managing the committee that selects the recipient of the Remsen award, the most prestigious chemistry award for the state of Maryland
 - *Member* **1994-present**

Publications

1. “The coronavirus macrodomain is required to prevent PARP-mediated inhibition of virus replication and enhancement of IFN expression” Grunewald, M.; Chen, Y.; Kuny, C.; Maejima, T.; Lease, R.*; **Ferraris, D.**; Aikawa, M.; Sullivan, C.; Perlman, S.; Fehr, A. **2019**, Accepted for publication *PLOS Pathogens*, **2019**, 15(5), e1007756.
2. “Structural and computational basis for potent inhibition of glutamate carboxypeptidase II by carbamate-based inhibitors” Barinka, C.; Novakova, Z.; Hin, N.; Bim, D.; **Ferraris, D.**; Duvall, B.; Kabarriti, G.; Tsukamoto, R.; Budesinsky, M.; Motlova, L.; Rojas, C.; Slusher, B.; Rokob, T.A.; Rulisek, L.; Tsukamoto, T. *Bioorg. Med. Chem.* **2019**, 27, 255-264.
3. “Design, synthesis and evaluation of potent and selective inhibitors of mono-(ADP-ribosyl)transferases PARP10 and PARP14” Holechek, J.*; Lease, R.*; Thorsell, A.-G.; Karlberg, T.; McCadden, C.*; Grant, R.*; Callahan, E.*; Schuler, H.; **Ferraris, D.** *Bioorg. Med. Chem. Lett.* **2018**, 28, 2050-2054.
4. “Design and Synthesis of Potent Inhibitors of the mono-(ADP-ribosyl)transferase, PARP14” Upton, K.*; Meyers, M.*; Thorsell, A.-G.; Karlberg, T.; Holechek, J.*; Lease, R.*; Schey, G.*; Wolf, E.; Lucente, A.; Schüler, H.; **Ferraris, D.** *Bioorg. Med. Chem. Lett.* **2017**, 27, 2907-2911.
5. “Synthesis, Characterization and Anti-neoplastic Activity of Bis-aziridine Dimeric Naphthoquinone – a Novel Class of Compounds with Potent Activity Against Acute Myeloid Leukemia Cells” Carter-Cooper, B. A.; Fletcher, S.; **Ferraris, D.**; Choi, E. Y.; Kronfli, D.; Dash, S.; Truong, P.*; Sausville, E. A.; Lapidus, R. G.; Emadi, A. *Bioorg. Med. Chem. Lett.* **2017**, 27, 6-10.
6. “Unprecedented Binding Mode of Hydroxamate-Based Inhibitors of Glutamate Carboxypeptidase II: Structural Characterization and Biological Activity” Novakova, Z.; Wozniak, K.; Jancarik, A.; Rais, R.; Wu, Y.; Pavlicik, J.; **Ferraris, D.**; Havlinova, B.; Ptacek, J.; Vavra, J.; Hin, N.; Rojas, C.; Majer, P.; Slusher, B.; Tsukamoto, T.; Barinka, C. *J. Med. Chem.* **2016**, 59, 4539-4550.
7. “Discovery of Orally Available Prodrugs of the Glutamate Carboxypeptidase II (GCPII) Inhibitor 2-Phosphonomethylpentane dioic acid (2-PMPA)” Majer, P.; Jancarik, A.; Krecmerova, M.; Tichy, T.; Tenora, L.; Wozniak, K.; Wu, Y.; Pommier, E.; **Ferraris, D.**; Rais, R.; Slusher, B. *J. Med. Chem.* **2016**, 59, 2810-2819.
8. “Discovery of 6-Diazo-5-oxo-norleucine (DON) Prodrugs with Enhanced CSF Delivery in Monkeys, a Potential Treatment for Glioblastoma” Rais, R.; Jančářík, A.; Tenora, L.; Nedelcovych, M.; Alt, J.; Englert, J.; Rojas, C.; Le, A.; Elgogary, A.; Tan, J.; Monincova, L.; Pate, K.; Adams, R.; **Ferraris, D.**; Powell, J.; Majer, P.; Slusher, B. *J. Med. Chem.* **2016**, 59, 8621-8633.
9. **Book Chapter in PARP Inhibitors for Cancer Therapy** Curtin, N., Sharma, R. Eds.: “Overview of PARP Inhibitor Design and Optimization”, **Ferraris, D.**, **2015**, pp. 183-203.
10. “6-Hydroxy-1,2,4-triazine-3,5(2H, 4H)-dione Derivatives as Novel D-Amino Acid Oxidase Inhibitors” Hin, N.; Duvall, B.; **Ferraris, D.**; Alt, J.; Thomas, A. G.; Rais, R.; Rojas, C.; Wu, Y.; Wozniak, K.; Slusher, B.; Tsukamoto, T. *J. Med. Chem.* **2015**, 58, 7258-7272.

11. "D-Amino-Acid Oxidase Inhibition Increases D-Serine Plasma Levels in Mouse but not in Monkey" Rojas, C.; Alt, J.; Ator, N. A.; Thomas, A. G.; Wu, Y.; Hin, N.; Wozniak, K.; **Ferraris, D.**; Rais, R.; Tsukamoto, T.; Slusher, B. *Neuropsychopharmacology* **2015**, 1-10.
12. "Design, Synthesis, and Pharmacological Evaluation of Fluorinated Tetrahydrouridine Derivatives as Inhibitors of Cytidine Deaminase" **Ferraris, D.**, Duvall, B., Delahanty, G., Mistry, B., Alt, J., Rojas, C., Rowbottom, C., Sanders, K., Schuck, E., Huang, K-C., Redkar, S., Slusher, B., Tsukamoto, T. *J. Med. Chem.* **2014**, 57, 2582-2588.
13. "δ-Thiolactones as Prodrugs of Thiol-Based Glutamate Carboxypeptidase II (GCPII) Inhibitors" **Ferraris, D.**, Majer, P., Ni, C., Slusher, C. E., Rais, R., Wu, Y., Wozniak, K., Alt, J., Rojas, C., Slusher, B., Tsukamoto, T. *J. Med. Chem.* **2014**, 57, 243-247.
14. "Peptidomimetics of Arg-Phe-NH₂ as Small Molecule Agonists of MAS-Related Gene C (MrgC) Receptors" Hin, N., Alt, J., Zimmermann, S., Delahanty, G., **Ferraris, D.** V., Rojas, C., Li, F., Liu, Q., Dong, X., Slusher, B., Tsukamoto, T. *Bioorg. Med. Chem. Lett.* **2014**, 22, 5831-5837.
15. "Dual Leucine Zipper Kinase (DLK) as a Therapeutic Target for Neurodegenerative Conditions" **Ferraris, D.**, Yang, Z., Welsbie, D. *Future Med. Chem.* **2013**, 5, 1923-1934.
16. "Kinetic Characterization of Ebselen, Chelerythrine and Apomorphine as Glutaminase Inhibitors" Thomas, A.G., Rojas, C., Tanega, C., Shen, M., Simeonov, A., Boxer, M., Auld, D.S., **Ferraris, D.**, Tsukamoto, T., Slusher, B. *Biochem. Biophys. Res. Comm.* **2013**, 438, 243-248.
17. "Synthesis of Kojic Acid Derivatives as Secondary Binding Site Probes of D-Amino Acid Oxidase" Raje, M., Hin, N., Duvall, B., **Ferraris, D.**, Berry, J., Thomas, A.G., Alt, J., Rojas, C., Slusher, B., Tsukamoto, T. *Bioorg. Med. Chem. Lett.* **2013**, 23, 3910-3913.
18. "Design, synthesis and pharmacological evaluation of bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES) analogs as glutaminase inhibitors" Shukla, K.; **Ferraris, D.**; Thomas, A.; Stathis, M.; Duvall, B.; Delahanty, G.; Alt, J.; Rais, R.; Rojas, C.; Gao, P.; Xiang, Y.; Dang, C. V.; Slusher, B.; Tsukamoto, T. *J. Med. Chem.* **2012**, 55, 10551-10563.
19. "Synthesis and Structure-Activity Relationships of 1-Hydroxy-1H-benzo[d]imidazol-2(3H)-ones as Inhibitors of D-Amino Acid Oxidase" Berry, J.; **Ferraris, D.**; Duvall, B.; Hin, N.; Rais, R.; Alt, J.; Thomas, A.; Rojas, C.; Hashimoto, K.; Slusher, B.; Tsukamoto, T. *Med. Chem. Lett.* **2012**, 10, 839-843.
20. "Design, Synthesis and Pharmacological Evaluation of Glutamate Carboxypeptidase II (GCPII) Inhibitors Based on Thioalkylbenzoic Acid Scaffolds" Stoermer, D.; Vitharana, D.; Hin, N.; Delahanty, G.; Duvall, B.; **Ferraris, D.**; Grella, B.; Hoover, R.; Rojas, C.; Shanholtz, M.; Smith, K.; Stathis, M.; Wu, Y.; Wozniak, K.; Slusher, B.; Tsukamoto, T. *J. Med. Chem.* **2012**, 55, 5922-5932.
21. "The Metabolic Profile of Tumors Depends on Both the Responsible Genetic Lesion and Tissue Type" Yuneva, M. O.; Fan, T. W. M.; Allen, T. D.; Higashi, R. M.; **Ferraris, D.**; Tsukamoto, T.; Mates, J. M.; Alonso, F. J.; Wang, C.; Seo, Y.; Chen, X.; Bishop, J. M. *Cell Metabolism* **2012**, 15, 157-170.
22. "Structure Activity Relationships of Glutamate Carboxy Peptidase II (GCP II) Inhibitors" **Ferraris, D.**; Shukla, K.; Tsukamoto, T. *Curr. Med. Chem.* **2012**, 19, 1282-1294.
23. "Development of a High-throughput Method for the Determination of Pharmacological Levels of Plasma D-Serine" Alt, J.; Rojas, C.; Wozniak, K.; Wu, Y.; **Ferraris, D.**; Tsukamoto, T.; Slusher, B. *Anal. Biochem.* **2011**, 419, 106-109.

24. "Recent Advances in the Discovery of D-Amino Acid Oxidase Inhibitors and Their Therapeutic Utility in Schizophrenia" **Ferraris, D.**; Tsukamoto, T. *Current Pharm. Des.* **2011**, *17*, 103-111.
25. "Inhibition of x_c - Transporter Mediated Cystine Uptake by Sulfasalazine Analogs" Shukla, K.; Thomas, A. G.; **Ferraris, D.**; Hin, N.; Sattler, R.; Alt, J.; Rojas, C.; Slusher, B.; Tsukamoto, T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6184-6187.
26. "Reduced BACE-1 Activity Enhances Clearance of Myelin Debris and Regeneration of Axons in the Injured Peripheral Nervous System" Farah, M. H.; Pan, B. H.; Hoffman, P. N.; **Ferraris, D.**; Tsukamoto, T.; Nguyen, T.; Wong, P.C.; Price, D. L.; Slusher, B. S.; Griffin, J. W. *J. Neurosci.* **2011**, *31*, 5744-5754.
27. "The Discovery and Structure-Activity Relationships of Indole-based Inhibitors of Glutamate Carboxypeptidase II" Grella, B.; Adams, J.; Berry, J.; **Ferraris, D.**; Majer, P.; Ni, C.; Shukla, K.; Shuler, S.; Slusher, B.; Stathis, M.; Tsukamoto, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7222-7225.
28. "Inhibition of Glutaminase Preferentially Slows Growth of Glioma Cells with Mutant IDH1" Seltzer, M.; Bennett, B. D.; Joshi, A.D.; Gao, P.; Thomas, A. G.; **Ferraris, D.**; Tsukamoto, T.; Rojas, C. J.; Slusher, B.; Rabinowitz, J. D.; Dang, C. V.; Riggins, G. J. *Cancer Res.* **2010**, *70*, 8981-8987.
29. "Evolution of Poly(ADP-ribose) Polymerase Inhibitors. From Concept to Clinic" **Ferraris, D.** *J. Med. Chem.* **2010**, *53*, 4561-4584.
30. "Co-Administration of a D-Amino Acid Oxidase Inhibitor Potentiates the Efficacy of D-Serine in Attenuating Prepulse Inhibition Deficits After Administration of Dizocilpine" Hashimoto, K.; Fujita, Y.; Horio, M.; Kunitachi, S.; Ivo, M.; **Ferraris, D.**; Tsukamoto, T. *Biol. Psychiatry*, **2009**, *65*, 1103-1106.
31. "Synthesis and Biological Evaluation of D-amino Acid Oxidase Inhibitors" **Ferraris, D.**; Duvall, B. Ko, Y.-S., Thomas, A. G.; Rojas, C.; Majer, P.; Tsukamoto, T. *J. Med. Chem.* **2008**, *51*, 3357-3359.
32. "Catalytic, Asymmetric Alkylation of Imines" **Ferraris, D.** *Tetrahedron*, **2007**, *63*, 9581-9597.
33. "Azetidine-based Inhibitors of Dipeptidyl Peptidase IV" **Ferraris, D.**; Belyakov, S.; Li, W.; Oliver, E.; Ko, Y.-S.; Calvin, D.; Lautar, S. *Current Topics in Medicinal Chemistry*, **2007**, *7*, 597-608.
34. "Novel Mechanism of Inhibition of Rat Kidney-type Glutaminase by Bis-2-(5-Phenylacetamido-1,2,4-Thiadiazolo-2-yl)Ethyl Sulfide (BPTES)" Robinson, M. M.; McBryant, S. J.; Tsukamoto, T.; Rojas, C.; **Ferraris, D.**; Hamilton, S. K.; Hansen, J. C.; Curthoys, N. P. *Biochem. J.* **2007**, *406*, 407-414.
35. "Glutamate production by HIV-1 infected human macrophage is blocked by the inhibition of glutaminase" Erdmann, N.; Zhao, J; Lopez, A; Herek, S.; Curthoys, N.; Hexum, T.D.; Tsukamoto, T.; **Ferraris, D.**; Zheng, J. *J. Neurochem.* **2007**, *102*, 539-549.
36. "Structure-Function Analysis of Water Soluble Inhibitors of Catalytic Domain of Exotoxin A from *Pseudomonas aeruginosa*" Yates, S.; Taylor, P. L.; Jorgensen, R.; **Ferraris, D.**, Zhang, J.; Anderson, G. R.; Merrill, A. R. *Biochem. J.* **2005**, *385*, 667-675.
37. "DPP IV Inhibitor Blocks Mescaline-induced Scratching and Amphetamine-induced Hyperactivity in Mice" Lautar, S. L; Rojas, C.; Slusher, B.; Wozniak, K. M.; Wu, Y.; Thomas, A. G.; Waldon, D.; Li, W.; **Ferraris, D.**; Belyakov, S. *Brain Res.* **2005**, *1048*, 177-184.

38. "Ketopyrrolidine and Ketoazetidines as Potent Dipeptidyl Peptidase IV (DPP IV) Inhibitors" **Ferraris, D.**; Ko, Y.-S.; Calvin, D.; Chiou, T.; Lautar, S.; Thomas, B.; Wozniak, K.; Rojas, C.; Kalish, V.; Belyakov, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5579-5583.
39. "Design and Synthesis of Poly(ADP-ribose)polymerase-1 (PARP-1) Inhibitors. Part 4: Biological Evaluation of Imidazobenzodiazepines as Potent PARP-1 Inhibitors for Treatment of Ischemic Injuries" **Ferraris, D.**; Pargas-Ficco, R.; Dain, D.; Ginski, M.; Lautar, S.; Lee-Wisdom, K.; Liang, S.; Lin, Q.; Lu, M.-X.-C.; Morgan, L.; Thomas, B.; Williams, L. R.; Zhang, J.; Zhou, Y.; Kalish, V. *Bioorg. Med. Chem.* **2003**, *11*, 3695-3707.
40. "Design and Synthesis of Poly(ADP-ribose)polymerase-1 (PARP-1) Inhibitors. Part 3: In Vitro Evaluation of 1,3,4,5-Tetrahydro[c][1,6]- and [c][1,7]-naphthridin-6-ones" **Ferraris, D.**; Pargas-Ficco, R.; Pahutski, T.; Lautar, S.; Huang, S.; Zhang, J.; Kalish, V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2513-2518.
41. "Design and Synthesis of Poly ADP-ribose polymerase-1 Inhibitors. 2. Biological evaluation of Aza-5[H]phenanthridin-6-ones as Potent, Aqueous-Soluble Compounds for the Treatment of Ischemic Injuries" **Ferraris, D.**; Ko, Y.-K.; Pahutski, T.; Pargas Ficco, R.; Serdyuk, L.; Alemu, C.; Bradford, C.; Chiou, T.; Hoover, R.; Huang, S.; Lautar, S.; Liang, S.; Lin, Q.; Lu, M. X.-C.; Mooney, M.; Morgan, L.; Qian, Y.; Tran, S.; Williams. L. R.; Wu, Q. Y.; Zhang, J.; Zou, Y.; Kalish, V. *J. Med. Chem.* **2003**, *46*, 3138-3151.
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43. "Catalytic, Enantioselective Alkylation of α -Imino Esters: The synthesis of Nonnatural $\alpha\alpha$ Amino Acid Derivatives" **Ferraris, D.**; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 69-79.
44. "Synthesis of Substituted 5[H]Phenanthridin-6-ones as Potent Poly(ADP-ribose)polymerase-1 (PARP1) Inhibitors" Li, J.-H.; Serdyuk, L.; **Ferraris, D.**; Xiao, G.; Tays, K. T.; Kletzly, P. W.; Li, W.; Lautar, S.; Zhang, J.; Kalish, V. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1687-1690.
45. "Catalytic, Enantioselective Alkylations of N,O- and N, N-Acetals and Hemiacetals" **Ferraris, D.**; Young, B.; Dudding, T.; Drury, W.; Lectka, T. *Tetrahedron* **1999**, *55*, 8869-8882.
46. "Nucleophilic Metal Complexes as Acylation Catalysts: Solvent-Dependent "Switch" Mechanisms Leading to the First Catalyzed Staudinger Reaction" Wack, H.; Drury, W. J.; Taggi, A. E.; **Ferraris, D.**; Lectka, T. *Org. Lett.*, **1999**, *1*, 1985-1988.
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53. "Copper(II)-Catalyzed Amide Isomerization: Evidence for N-Coordination" Cox, C.; **Ferraris, D.**; Murthy, N. N.; Lectka, T. *J. Am. Chem. Soc.* **1996**, *118*, 5332-5333.

Issued Patents

1. 'Certain Compounds, Compositions and Methods' Hamilton, G. S.; Tsukamoto, T.; **Ferraris, D. V.**; Duvall, B.; Lapidus, R. U. S. Patent 8,268,800, Sept. 18, 2012.
2. 'Compounds and their Uses' **Ferraris, D. V.**; Li, J.-H.; Kalish, V.; Zhang, J. U.S. Patent 7,915,280, March 29, 2011.
3. 'Compositions and Methods for Treating Cancer' Belyakov, S.; Duvall, B.; **Ferraris, D. V.**; Hamilton, G.; Vaal, M. U.S. Patent 279,977, Nov. 4, 2010.
4. 'Compounds, Derivatives, Compositions, Preparation and Usage' Xu, W.; **Ferraris, D. V.**; Li, J.-H.; Kalish, V. U. S. Patent 7,247,641, July 24, 2007.
5. 'Compounds and their uses' **Ferraris, D. V.**; Li, J.-H.; Kalish, V.; Zhang, J. U.S. Patent 7,235,557, May 26, 2007.
6. 'Compounds and their uses' **Ferraris, D. V.**; Li, J.-H.; Kalish, V.; Zhang, J. U.S. Patent 6,887,996, May 3, 2005.
7. 'Sulfonamide and Carbamide Derivatives of 6(5H)phenanthridones and their uses' Li, J.-H.; Kalish, V.; Zhang, J.; Serdyuk, L. E.; **Ferraris, D. V.**; Xiao, G.; Kletzly, P. W.; U. S. Patent 6,723,733, April 20, 2004.
8. 'Symmetrically Substituted Aromatic Compounds and Pharmaceutical Compositions for Inhibiting poly(ADP-ribose) Glycohydrolase and Methods for Their Use' Li, J.-H.; **Ferraris, D. V.**; Kletzly, P.; Li, W.; Wang, E. Y.; Xing, A.; Xu, W.; Zhang, J.; U. S. Patent 6,635,786, Oct. 21, 2003.

Invited Presentations

- Stevenson University, **October 2015**, Title: *The Evolving Role of Medicinal Chemists in Drug Discovery*
- Johns Hopkins Medical School, **June 2013**, Title: *Drug Discovery at the Brain Science Institute: Glutamate Carboxypeptidase II as a therapeutic target*
- St. Johns University, **December 2012**, Title: *Poly(ADPribose)polymerases as Therapeutic Targets*
- Celgene Inc., **June 2012**, Title: *Poly(ADPribose)polymerases as Therapeutic Targets*

- Lafayette College, **September 2012**, Title: *Current Landscape of Drug Discovery Research: Challenges and Opportunities*
- Johns Hopkins University, **April 2009**, Title: *DAAO Inhibitors for the Treatment of Schizophrenia*
- 227th American Chemical Society National Meeting, **April 2004**, Title: *PARP-1 Inhibitors as Neuroprotective Agents*

EXHIBIT 12

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

TORRENT PHARMACEUTICALS LIMITED and TORRENT PHARMA INC.,

Defendants/Counterclaim-
Plaintiffs.

Civil Action No. 17-3186-SRC-CLW

(CONSOLIDATED)

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

INDOCO REMEDIES LTD.,

Defendant/Counterclaim-Plaintiff.

Civil Action No. 17-7301-SRC-CLW

**REPLY REPORT OF DANA FERRARIS, PH.D.
REGARDING THE INVALIDITY OF U.S. PATENT
NOS. 7,807,689; 8,288,539; AND 8,173,663**

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I. INTRODUCTION

1. My name is Dana Ferraris, and I provided my “Opening Expert Report of Dana Ferraris, Ph.D. Regarding the Invalidity of U.S. Patent Nos. 7,807,689; 8,288,539; and 8,173,663,” on June 14, 2019 (“Opening Report”) on behalf of Defendants, Indoco Remedies Ltd. (“Indoco”) and Torrent Pharmaceuticals Limited and Torrent Pharma Inc. (collectively, “Torrent”) to assist Defendants with their positions regarding the claims of U.S. Patent Nos. 7,807,689; 8,288,539; and 8,173,663.

2. My Opening Report included a description of my qualification, education, professional experience, prior testimony, and compensation. (Opening Report ¶¶ 8-19.)

3. Dr. David E. Nichols, expert of Plaintiffs Takeda Pharmaceutical Company Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Limited (collectively “Takeda”), served a Rebuttal Expert Report on July 19, 2019 (“Nichols Report”) that responded to my Opening Report.

4. I have reviewed the Nichols Report, the exhibits to his report, and all materials referenced therein.

5. After my review of the Nichols Report, I maintain my position as presented in my Opening Report that the alleged inventions in claims 1, 3, 4, 9, 11-12, 43, and 49 of U.S. Patent No. 7,807,689 (“the ’689 patent”); claims 2-3, 5-7, 9, 11, 15, and 18 of U.S. Patent No. 8,288,539 (“the ’539 patent”); and claims 1, 4, 6-8, 10, 12, 14-17, 19-21, 27, and 29 of U.S. Patent No. 8,173,663 (“the ’663 patent”) would have been obvious to a person having ordinary skill in the art (“POSA”) in March 2004, based on the references cited in my Opening Report, in addition to the general knowledge available in the field of medicinal chemistry.

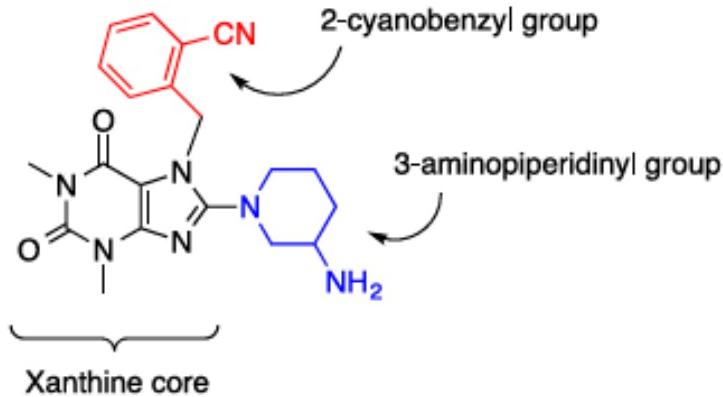
6. My specific responses to opinions provided in the Nichols Report are provided below. I reserve the right to comment further on Dr. Nichols' Report as needed. As this case progresses, I may review additional information.

7. In forming my opinions, I considered and relied on my education, background, experience, training, and skills that I have accumulated over the course of my career. I have also considered references and relevant scientific literature in support of the opinions set forth this Reply and have indicated those references in footnotes and attached in Exhibit A. Such references are to be considered as part of my Materials Considered.

II. SUMMARY

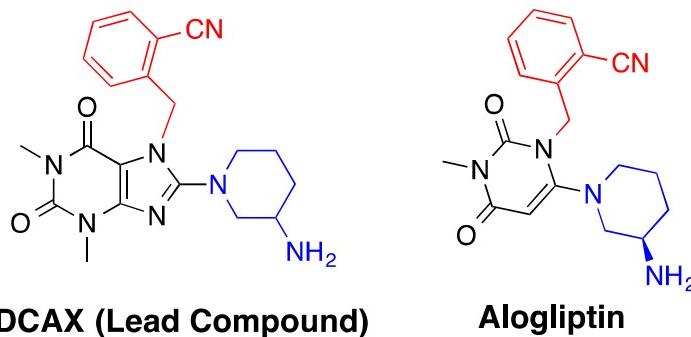
8. In my Opening Report, I stated my opinion that a person of ordinary skill in the art would have found subject matter of each asserted claim of the '689 patent, the '539 patent, and the '663 patent invalid as obvious in view of certain prior art documents cited in the Opening Report. My opinion is supported, in part, by the prior art documents and the relevant scientific literature cited in my Opening Report. My opinion, as set forth fully in my Opening Report, is based, in part, on the fact that prior to the filing of the '689 patent (*i.e.*, prior to March 2004) a promising compound was independently discovered and disclosed by both Boehringer Ingelheim and Novo Nordisk in two patent filings, International Publications WO 2002/068420 A1 and WO 2003/004496 A1, respectively. Dr. Nichols refers to this lead compound in his report as "DCAX," an abbreviation I will similarly adopt for efficiency.

9. The structure of DCAX, (*i.e.*, 1,3-dimethyl-7-(2-cyanobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine), is set forth below:



1,3-dimethyl-7-(2-cyanobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine (DCAX)

10. As illustrated below, with the lead compound DCAX shown on the left and alogliptin shown on the right, DCAX is remarkably similar to alogliptin (*e.g.*, the xanthine core in the above compound is replaced with a uracil core in alogliptin, in black in the Figure below).



11. Because DCAX was reported to be biologically active ($IC_{50} = 10 \text{ nM}$) as a DPP-IV inhibitor and had key structural motifs that were common to DPP-IV inhibitors, as I explained in my Opening Report and elaborate further upon in this Reply, DCAX would have been a lead compound to a person of ordinary skill in the art (POSA), particularly given its unusual position of being identified by two separate pharmaceutical companies, Novo Nordisk and Boehringer Ingelheim, investigating DPP-IV inhibitors.

12. Further, in my opinion, not only would DCAX have been a natural starting point (*i.e.*, a lead compound) to a person of ordinary skill in the art for further drug design, it would

have been obvious to make the simple modifications to DCAX to yield alogliptin. At the time of filing of the '689 patent, the crystal structure of DPP-IV enzyme, and its active site was known in the prior art. Certainly, with knowledge of the crystal structure and the active site of the DPP-IV enzyme, replacing the xanthine core from the biologically active compound, (*i.e.*, DCAX), with a uracil core would have been an obvious consideration to a person of ordinary skill in the art. Indeed, from my experience and to my knowledge as a medicinal chemist the substitution of such ring cores in drug design and development was known at the time. For example, both U.S. Patent Nos. 5,142,051 and 5,780,476, include uracil and xanthine as preferred interchangeable heterocyclic ring cores.

13. Moreover, as detailed in my Opening Report, the prior art disclosed other DPP-IV inhibitory compounds containing a xanthine core that also included both 2-cyanobenzyl and 3-aminopiperidinyl groups. These compounds exhibited DPP-IV inhibitory activity with IC₅₀ values of 16 nM and 32 nM, respectively. (*See* CA 2 946 249 at 34, 137, 138). In my opinion, the POSA would recognize that these compounds had favorable IC₅₀ values that could likely be attributed to the presence of 2-cyanobenzyl and 3-aminopiperidinyl groups also found in DCAX, a compound with DPP-IV inhibitory activity of 10 nM. As a result of this information, the POSA would have recognized that the state of the art at the time of the invention strongly indicated that both the cyano group (as the 2-cyanobenzyl) and the 3-aminopiperidinyl group were important structural elements that lead to the increased inhibitory potency against DPP-IV.

III. DR. NICOLS' DESCRIPTION OF A PERSON OF ORDINARY SKILL IN THE ART AND THEIR KNOWLEDGE AND SKILL SET IS INCORRECT

14. Dr. Nichols does not appear to disagree with my basic definition of a POSA (Nichols Report at ¶ 44).

15. Instead, Dr. Nichols opines that my report applies and relies on a person having higher skills and more knowledge than the POSA in March 2004. (Nichols Report at ¶ 44.) I disagree. It is my position that the POSA that Dr. Nichols describes would not be responsible for any drug development or design, but instead would be carrying out instructions of such a person. In my opinion the POSA would have the skills and knowledge of a typical medicinal chemist involved in developing new drugs (*i.e.* new chemical entities).

16. Although Dr. Nichols states that a POSA would have an advanced degree in chemistry or medicinal chemistry with at least one to two years of experience or a B.S. in organic or medicinal chemistry and extensive experience of five to ten years in a drug discovery program, his report applies and relies upon a person that merely has a chemistry degree (not medicinal chemistry) and little to no experience in drug discovery.

17. I further disagree with Dr. Nichols' statement that a "POSA would not be able to extract key structure-based information from peptidic-like substrate/inhibitor DPP-IV enzyme crystal structures, extrapolate the recognition and interactions identified between the DPP-IV enzyme active site and the **peptidic**-like substrate/inhibitor, and then apply that information to the designing of **non-peptidic** DPP-IV inhibitors." (Nichols Report at ¶ 44 (emphasis in original).) Dr. Nichols' description is misleading. This set of skills is not required for a POSA. At the time of invention, structure-based drug design techniques were considerably evolved, and it was only necessary for the POSA to understand substrate specificity of the DPP-IV enzyme and its mode of interaction with substrates to design a non-peptide based DPP-IV inhibitor. It was not necessary for POSA to have knowledge of the 3D-crystal structure of DPP-IV enzyme-**non-peptide** DPP-IV inhibitor/substrate complex for designing non-peptide DPP-IV inhibitors. In fact, at the time of invention the knowledge of the three-dimensional structure of the biological

target (*i.e.*, DPP-IV enzyme) was determined by X-ray crystallography, as reported in Engel and Aertgeerts. Both, Engel and Aertgeerts describe the active site of the DPP-IV enzyme, and discuss strategies for rational design of further DPP-IV inhibitors. This provided ample information to the POSA to design any DPP-IV inhibitor, including a non-peptide DPP-IV inhibitor. In addition, a POSA would not have required knowledge of the 3D-crystal structure of DPP-IV enzyme-non-peptide DPP-IV inhibitor/substrate complex for designing non-peptide DPP-IV inhibitors because for many years, before crystal structures were readily available, medicinal chemists conducted their analysis by evaluating the structure activity relationships (SAR) and trends associated with various potential candidates. This fact is ignored by Dr. Nichols. Notwithstanding the fact that there was not a crystal structure of non-peptidic compounds interacting with the DPP-IV enzyme, the POSA here nevertheless would have developed a valid hypothesis that certain groups on a candidate compound could bind to the active site serine known to be involved in peptidic-like substrate's interactions with DPP-IV. For example, the POSA would not need X-ray data of non-peptidic compounds to infer that a nitrile group present in a non-peptide DPP-IV inhibitor might bind to the active site of DPP-IV enzyme given the unique prevalence of this group in a variety of DPP-IV inhibitors such as those reported in Evans and Weideman. A POSA would know that compound 1(2) ($IC_{50} = 82\text{ nM}$) in the '730 patent is identical to DCAX except that for the absence of a nitrile. Because compound 1(2) is 8 fold less potent than DCAX, a POSA would hypothesize that the nitrile is absolutely essential to binding, just like so many other DPP-IV inhibitors at the time. In addition, a POSA would know that a primary amine is part of the pharmacophore of DPP-IV inhibitors because DPP-IV cleaves the penultimate peptide bond from the N-terminus of its substrates, (all of which have a primary amine at the N-terminus). In my opinion, Dr. Nichols' Report provides a narrow

and unrealistic understanding of the steps undertaken by the POSA in rational drug design and what skills would be necessary for drug design.

18. Dr. Nichols also opines that a POSA would not change the scaffold of DCAX particularly given that “it was well-known that changing even a single atom in a biologically-active molecule can drastically change not only its potency, but also the type of pharmacology it possesses.” (Nichols Report at ¶ 53, *see also* ¶ 55.) I disagree. Dr. Nichols’ statements are not correct, in part, because Dr. Nichols misunderstands the techniques associated with new drug development. Indeed, the examples cited by Dr. Nichols as support for his position that a change in a single molecule can impact drug properties are not relevant to the current analysis. The first example (Tagat *et al.*) does not explain the dramatic change referred to by the author. For the second and third examples, the change of one atom resulted in exactly what a POSA would expect. The second example (Frantz *et al.*) reported that the addition of fluorine by replacing hydrogen at the 4-position of phenyl ring improved oral availability and drug half-life. It was well-known that adding fluorine to a molecule provides compounds having higher oral bioavailability, for instance the fluoroquinolones obtained by adding fluorine at position 6 improved the pharmacokinetic profile such as the oral bioavailability of the compounds. The third example (Classen *et al.*) addresses the addition of deuterium atoms and its effect on tolerance and efficacy, qualities known to be associated with this substitution. (*See e.g.*, PCT Publication WO 95/26325 (Publication date : Oct. 5, 1995.)

19. In my opinion, the POSA developing a new drug candidate would take a rational approach to drug design. Rational drug design refers to the development of new drug candidates based on the study of the structures of the therapeutic targets. The role of rational drug design is

to use a methodological approach to developing a new drug.¹ During rational drug design, researchers take general steps to create a new drug. Such steps include, for example: identifying a receptor or enzyme that is relevant to a disease target (*e.g.*, prior to the filing date of the invention, it was known that the inhibition of DPP-IV enzyme provides for a promising treatment for type II diabetes); elucidating the structure and function of this receptor or enzyme using X-ray crystallography and/or NMR (*e.g.*, the x-ray crystal structure of DPP-IV was known prior to the filing date of the invention), and using this information in order to design a drug molecule that interacts with the receptor or enzyme in a therapeutically beneficial way. Substrate-based drug design (*i.e.*, designing a drug based on what was understood about the substrate it would bind to) was a very successful means of developing a drug target. No X-ray of the binding between the proposed inhibitor and the enzyme was necessary, just knowledge about the substrate (in DPP-IV's case, specific peptides were known to be part of the binding site) and its mechanism of action (for DPP-IV, it was known to be a serine protease, which was well known and understood at the time). So the change to an existing biologically active molecule exhibiting DPP-IV inhibitory activity could be made in consideration of the knowledge already documented in the art.

20. Dr. Nichols argues that the compounds cited in my Opening Report all contain xanthine scaffold, and therefore, a POSA will recognize that xanthine core is the “central feature” of the pharmacophore. (Nichols Report at ¶ 56.) The Nichols’ Report highlights the term “pharmacophore,” reciting definition of the term from Dror 2004² as “molecular framework that carries (*phoros*) the essential features responsible for a drug’s (*pharmacon*) biological

² Dror, Oranit, et al., *Predicting Molecular Interaction in silico: I. A Guide to Pharmacophore Identification and its Applications to Drug Design*, 11 CURRENT MED. CHEM. 71 (2004) (“Dror 2004”)

activity.” (*Id.*) However, Dror 2004 adds that presently the term pharmacophore has been expanded to refer to the 3D arrangement of features that enable a molecule to exhibit a specific biological activity. Dror 2004 also adds that molecules are active in particular receptor if they possess or carry the features that interact favourably with the receptor. (*See* Dror 2004 at 71).

This discussion from Dror 2004 cited in Nichols report clarifies that this reference does not indicate central core of a pharmacophore being very important. As explained in my Opening Report, it is entirely within the purview of the POSA to replace scaffold (*i.e.*, central core) of one biologically active molecule with another scaffold (*i.e.*, central core) to obtain a compound that retains biological activity exhibited by the starting biologically active compound. For example, replacing one heterocycle with another heterocycle (*e.g.*, replacing a xanthine with a uracil core) is regularly performed by medicinal chemists. Once a medicinal chemist recognizes the likely pharmacophore (a POSA would recognize from the teaching of Dror 2004 that it is not just the central scaffold but the functional features of the molecule that interact favorably with the receptor or enzyme that are critical for biological activity of the molecule) and therefore, a POSA would consider retaining the critical features of the lead compound, and change other components such as the central scaffold of the lead compound to so as retain the desired biological activity in the resulting compound. In other words, these modifications extend to replacing and modifying scaffolds if it is determined that their role does not appear to be critical for binding to the target and the therapeutic activity. This concept was known, and in practical use well before the critical date for the patents-in-suit. In fact, Dr. Nichols himself has co-authored papers where he reviews the pharmacophore of dopamine agonists where the central ring was modified while keeping the other pharmacophoric elements intact.³

³ Mottola, D., et al., *Conformational Analysis of D1 Dopamine Receptor Agonists: Pharmacophore*

21. Moreover, in contrast to Dr. Nichols statements, it is my opinion that a POSA would have recognized that the least likely part of the pharmacophore involved in imparting the desired DPP-IV inhibitory activity is the xanthine core of the compound. The benzonitrile (as well as nitriles in general) were already established as part of the DPP-IV pharmacophore as was the primary amine. In addition, xanthines were fraught with intellectual property issues, particularly patent protection issues, which a POSA would have considered in designing new drug treatments. Xanthines had been used as a known scaffold for decades and were very common in a variety of drug discovery projects (including development as phosphodiesterase inhibitors, antimicrobial agents, antitumor agents, etc.).

22. I further disagree with Dr. Nichols that a POSA would find a scaffold change “counterintuitive” and would find it “impossible to predict the resulting effects” as well as his opinion that a scaffold change would create a “complete disruption of the requisite three-dimensional arrangement of the molecular components of the pharmacophore” (Nichols Report at ¶ 58.) Drug design relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.⁴ In other words, a POSA could work backwards and a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Based on the properties reported for other

Assessment and Receptor Mapping, 39 J. MED. CHEM. 285-296 (1992) (evaluating several dopamine receptor with different central cyclic cores, including a seven-membered ring containing nitrogen, multiple six membered rings with oxygen, and a bicyclic ring containing nitrogen.) Blair, J., et al., *Thieno [3,2-b]- and Thieno [2,3-b]pyrrole Bioisosteric Analogs of the Hallucinogen and Serotonin Agonist N, N-Dimethyltryptamine*, 42 J. MED. CHEM. 1106-1111 (1999) (swapping an aromatic (phenyl ring) with a thiophyl ring.)

⁴ Guner OF (2000). Pharmacophore Perception, Development, and use in Drug Design. La Jolla, Calif: International University Line.

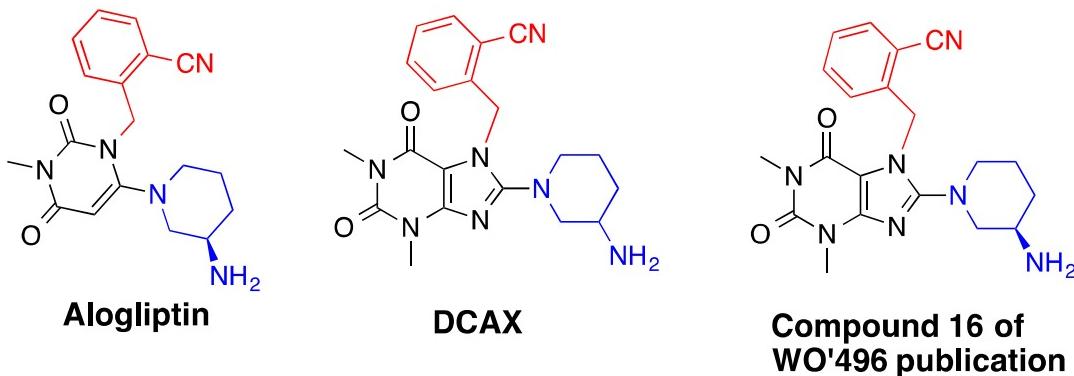
potential DPP-IV compounds, such as the potency or the binding affinity of certain functional groups to the target, I do not believe a POSA would consider the central scaffold as imparting biological activity to DCAX, and accordingly, I do not believe a POSA would find it counterintuitive at all to replace such a scaffold. In doing so, a POSA would have reasonable likelihood of successfully retaining, and likely improving, the promising properties of DCAX. For example, in Dror 2004, it is expressly stated that the power of pharmacophore-based methods for lead generation lies in their ability to suggest a diverse set of compounds potentially possessing a desired biological activity, but *which have totally different chemical scaffolds.* (See Dror 2004 at page 72 (emphasis added).)

IV. THE CLAIMS OF THE '689 PATENT, THE '539 PATENT, AND THE '663 PATENT ARE OBVIOUS.

23. As an initial matter, the Nichols Report mischaracterizes the substance of my opinion. My opinion was focused on whether the invention recited in claims 1, 3, 4, 9, 11-12, 43, and 49 of the '689 patent, claims 2-3, 5-7, 9, 11, 15, and 18 of the '539 patent, and claims 1, 4, 6-8, 10, 12, 14-17, 19-21, 27, and 29 of the '663 patent were obvious to a POSA from, *inter alia*, the disclosures of publicly available documents and the general knowledge in the art in March 2004. (Op. Rep. at ¶¶ 20-22.)

A. Compound 1(121) is an Obvious Choice of Lead Compound

24. Dr. Nichols goes to great lengths to discuss in his opinion why “neither the xanthine compounds of the WO '496 publication and the CA '730 patent, nor DCAX specifically, are structurally homologous to Alogliptin.” (Nichols Report at ¶ 66; *see also* ¶ 84 (stating that DCAX “it is certainly not structurally similar to Alogliptin”)). However, the POSA could very easily see the obvious structural similarities between the DCAX lead compound and the obvious claimed compound, encompassing alogliptin. The structures are illustrated below:



25. As is clear from this comparison, DCAX and Alogliptin are quite similar. The similarities include: (i) a cyanobenzyl group (shown in red) – this group is bound to the nitrogen atom of the central core in both compounds; and (ii) a 3-amino piperidine (shown in blue) – this moiety is bound to the carbon adjacent to the cyanobenzyl group in both compounds. The similarity between the two compounds is the molecular structure similarity.

26. Dr. Nichols also argues that I have used hindsight to identify the class of xanthine core compounds. He further states that “[i]t should be noted that Wiedeman does not describe the compounds containing a xanthine core as ‘one of the most promising DPP-IV inhibitors’ among the ‘non-peptidic DPP-IV inhibitors’ - that is purely Dr. Ferraris’ characterization.” (Nichols Report at ¶ 62.) I wish to clarify my statement in my Opening Brief. The CA ’730 patent discloses the results obtained from testing 31 compounds for their ability to inhibit DPP-IV activity. (CA ’730 patent, cols. 98-100). Five test compounds are found to exhibit DPP-IV inhibitory activity in IC₅₀ value ranging between 2 nM and 10 nM, indicative of the compounds being highly potent DPP-IV inhibitors. The POSA would recognize the IC₅₀ values for any test compound in a range of 2 nM to 10 nM would be considered highly potent and thus a promising group of inhibitors to consider in further drug design.

Compound	IC50 ⁵	Structure
Compound 1(121): 1,3-dimethyl-7-(2-cyano-benzyl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 197:13)	10 nM	
Compound 2(28): 1-(2-phenyl-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 204:24-25)	5 nM	
Compound 2(88): 1-[2-(3-cyanomethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 214:26-27)	6 nM	
Compound 2(119): 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine (CA '730 patent, Col. 220:6-7)	2 nM	

⁵The IC₅₀ data is found in CA '730 patent at cols. 99-100.

Compound	IC50 ⁵	Structure
Compound 2(136): 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-aminopiperidin-1-yl) xanthine (CA '730 patent, Col. 223:14-15)	3 nM	

27. Dr. Nichols further opines that “Dr. Ferraris’ selection of xanthine-based compounds is based on hindsight. Without providing any rationale or explanation for the selection, Dr. Ferraris chooses the class of xanthine compounds over the entire class of various known peptidic inhibitors—a class that bears at least some resemblance to the agents bound within DPP-IV enzyme crystallographic structures as of March 2004—and over the other potent non-peptidic inhibitor classes discussed in Wiedeman.” (Nichols Report at ¶ 70.) In my opinion, a POSA would not consider peptide like DPP-IV inhibitors as lead compound(s) for optimization because the prior art, for example Lambeir,⁶ discloses that development of proline-specific dipeptidyl-peptidases inhibitors are problematic because of their inactivation due to intramolecular cyclization. Further, Lambeir has identified problems such as instability, toxicity, lack of selectivity, hydrolysis by DPP-IV or weak inhibition associated with the peptide DPP-IV inhibitors listed in Table 2. (*See* Lambeir at pages 220-222). Also, the WO ‘496 publication in the background of invention section specifies that several compounds have been shown to inhibit DPP-IV, but all of these have limitations in relation to the potency, stability, selectivity, toxicity, and pharmacodynamic properties. Further, in reference to the xanthine (purine) compounds covered in it, WO ‘496 publication specifies that the compounds are not amino acid derivatives,

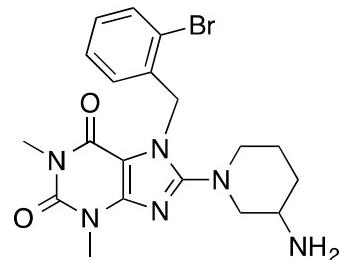
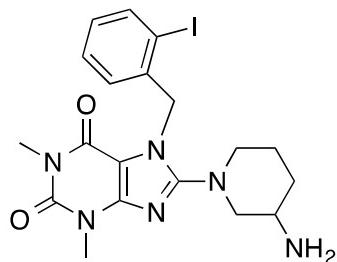
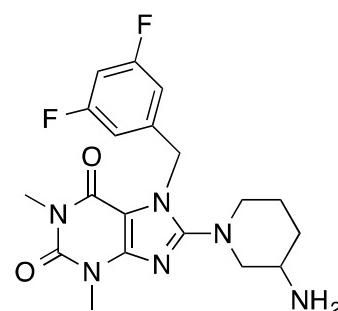
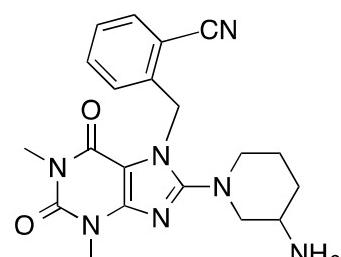
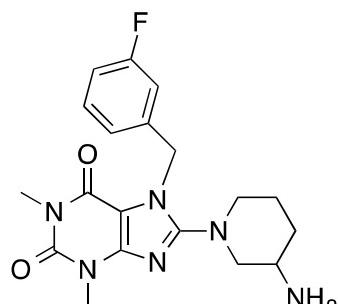
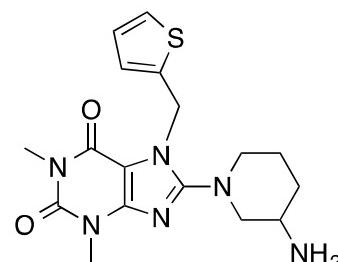
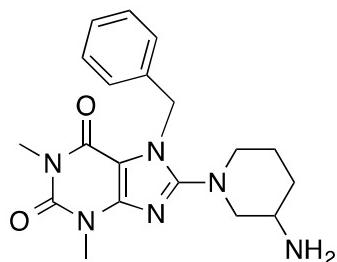
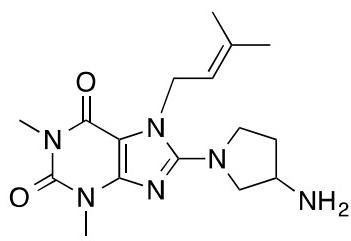
⁶ Lambeir A., Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV, CRIT. REV. CLIN. LAB. SCI. 209-294, at 220, 222 (2003).

such as the known DPP-IV inhibitors, and that they represent novel solutions to the problem of finding an optimal DPP-IV inhibitor. Such disclosures in the prior art will automatically attract a POSA's attention to xanthine compounds in consideration of further development of DPP-IV inhibitors. This establishes that my selection of xanthine derivatives as DPP-IV inhibitors is not based on hindsight but in consideration of the teachings in the prior art. Moreover, my selection of the CA '730 patent and the WO '496 publication and the xanthine class of non-peptidic inhibitors is based not on hindsight but rather on the fact that these documents are material prior art compelling DPP-IV inhibition. In my opinion, a POSA would have been aware of these papers, and the disclosure of compounds with promising IC₅₀ values would lead the POSA to recognize that the "preferred" compounds disclosed in these patent documents qualify as lead compound candidates for further investigation.

28. Dr. Nichols also disagrees that a POSA would recognize DCAX as a lead compound. The Nichols Report states that "the CA '730 patent compounds of Examples 1, 1(2), 1(9), 1(10), 1(121), 1(124), 1(138), and 10(135) overlap with the WO '496 publication compounds of Examples 2-4 (racemate, S-isomer, and R-isomer), Example 17 (R-isomer), Example 103 (R-isomer), Example 44 (racemate), Example 1 (racemate), Example 46 (racemate), Example 9 (racemate), and Examples 10 (racemate) and 20 (R-isomer), respectively." (Nichols Report at ¶ 86.) The Nichols Report further states that "considering that overlapping compound 1(2), and not DCAX, is included in the 38 preferred compounds listed in the CA '730 patent, a POSA would more likely select compound 1(2) as a lead compound than DCAX." (Nichols Report at ¶ 86.) I strongly disagree that a POSA would draw the conclusions that Dr. Nichols proposes.

29. Below are the 8 overlapping compounds in the '730 and '496 patents and their

respective inhibition constants.



30. In my opinion, Dr. Nichols again takes a very narrow approach to drug discovery that is not consistent with the level of skill of the POSA to choose Example 1(2) as the more likely lead. Of the compounds identified by Dr. Nichols (Nichols Report at ¶ 86) DCAX (Example 1(121)) is by far the most obvious choice. As an initial point, compounds 1(1), 1(9), 1(10), 1(124), 1(138) and 10(135) do not have any IC₅₀ data, so a POSA would not recognize

these as preferred compounds given that they do not have knowledge of their activity. There are only two overlapping compounds with biological data indicating potency of the compounds.

With respect to Dr. Nichols' assertion that "a POSA would more likely select compound 1(2) as a lead compound than DCAX," I note that Compound 1(2) has an IC₅₀ of 82 nM and is a very close derivative of Compound 1(121), i.e. DCAX. In fact, the only difference is the nitrile group present at position 2 of the phenyl of the benzyl group at position 7 of the xanthine core. Compound 1(121) (DCAX), on the other hand, has an IC₅₀ value of 10 nM. By comparing the IC₅₀ values of Compounds 1(2) and 1(121), a POSA would recognize that Compound 1(121) has a significantly lower IC₅₀ value and accordingly may be a better lead compound. Moreover, comparing Compounds 1(2) and 1(121)/DCAX, the POSA would deduce that the nitrile likely contributes to about an 8 fold boost in potency making it DCAX an ***even more obvious lead compound*** and supporting the hypothesis that the POSA would maintain a nitrile group in selecting a lead compound.

31. Dr. Nichols further disagrees with the choice of DCAX as a lead because it "is the **least active** of the 5 selected compounds. Without more, a POSA would not conclude that DCAX could be a lead compound based upon a mere overlapping disclosure." (Nichols Report at ¶ 87 (emphasis in original).) This logic is, again, not consistent with the level of skill of the POSA. In my opinion the POSA would not discount any of the 5 selected compounds because the difference in IC₅₀ values from IC₅₀ of 2 nM to an IC₅₀ of 10 nM is negligible. The variability of the DPP-IV assay at the time was anywhere from plus or minus 10-25% of the IC₅₀ value.⁷ In

⁷ See, e.g., Villhauer, E., et al., *I-[2-[5-Cyanopyridin-2-yl]amino]-ethylamino]acetyl-2-(S)-pyrrolidine-carbonitrile: A Potent, Selective, and Orally Bioavailable Dipeptidyl Peptidase IV Inhibitor with Antihyperglycemic Properties*, 45 J. MED. CHEM. 2362-2365 (2002); Senten, K., et al., *Design, Synthesis, and SAR of Potent and Selective Dipeptide-Derived Inhibitors for Dipeptidyl Peptidases*, 46 J. MED. CHEM. 5005-5014 (2003).

the absence of a standard deviation it would be folly to disregard a compound based on the differences observed in the most potent compounds of the CA '730 patent. For example, a 6 nM compound plus or minus 2 nM would be in the range of 4-8nM while a 10 nM compound plus or minus 2nM would be 8-12nM, overlapping on the low end with the 6 nM compound.

32. Dr. Nichols further states that “Dr. Ferraris does not indicate why a potency threshold of an IC₅₀ value of 10 nM was selected. That selection appears to be, again, guided by hindsight to include DCAX among the list of possible lead compounds. In fact, Dr. Ferraris selects Compound 1(121) (*i.e.*, DCAX)—the **least active** compound in inhibiting DPP-IV of the five—as his ‘lead compound.’” (Nichols Report at ¶ 93 (emphasis in original).) Again, Dr. Nichols opinion is not consistent with drug development or the level of skill of the POSA. Medicinal chemists typically group compounds in orders of magnitude (*e.g.* 1-10nM, 10-100nM, 100-1000nM etc.). Dr. Nichols opinion that a POSA would reject a compound with an IC₅₀ value of 10 nM in favor of an IC₅₀ value of 2 nM is incorrect and inconsistent with how medicinal chemists are trained to conduct drug discovery. Because biological and enzymatic assays often have high variability, as was known for the DPP-IV assays at the time, a POSA would recognize and consider compounds having activity in the first order of magnitude to be roughly similar in enzymatic potency and thus would look to other indications for their choice of lead.

33. I further disagree with Dr. Nichol’s conclusion that “a POSA would have assumed that the higher IC₅₀ value for DCAX (*i.e.*, less potent) compared with the first four compounds that have a methyl butenyl group meant that DCAX’s 2-cyanobenzyl group was not as effective as the methyl butenyl group.” (Nichols Report at ¶ 94.) Again, this comment is inconsistent with how medicinal chemists conduct drug discovery. As noted above the error of

the assay is likely in the range of plus or minus 1-5 nM, so a POSA would say that all of the 5 compounds are comparably potent inhibitors of DPP-IV.⁸ I thus disagree with Dr. Nichols opinion that DCAX is dramatically less potent. Moreover, Compound 1(2) (the compound that Dr. Nichols opined would be more likely selected as a lead compound than DCAX) has an IC₅₀ of 82 nM and is a very close derivative of DCAX (the only difference is the nitrile). By comparison Compound 1(121)/DCAX has an IC₅₀ value of 10 nM. By comparing Compounds 1(2) and 1(121)/DCAX, a POSA would recognize that the nitrile conveys about an 8 fold boost in potency making it an even more obvious lead compound than the compounds containing methyl butenyl groups. I further note that two other compounds disclosed in the CA '730 patent that have methyl butenyl groups at position 7 of the xanthine core, compound 1(19) and 1(30) show extremely poor activity (2770 nM and 2050 nM). Given the large variation in activity exhibited by compounds having methyl butenyl groups, a POSA would be skeptical as to value of that substituent compared to the nitrile group.

34. Dr. Nichols also argues "when the electrophilicity of the cyano groups is considered, as evaluated in Oballa, Renata M., et al., "[a] generally applicable method for assessing the electrophilicity and reactivity of diverse nitrile-containing compounds," Bioorganic & Medicinal Chemistry Letters 17 998-1002 (2007), a POSA would recognize the cyano group attached to a phenyl ring, e.g., the 2-cyanobenzyl group of Alogliptin . . . , is a poorer electrophile - i.e., less likely to react with the Serine 630 hydroxyl acting as a nucleophile-than the cyano group attached a carbon adjacent to an amide nitrogen, such as in the 2-cyanopyrrolidine of FE-999011." (Nichols Report at ¶ 114.) In my opinion, this reliance on a publication well after the filing date to purportedly suggest that the POSA would not choose a cyanobenzyl group is a

⁸ *Id.*

complete *non sequitur*. Regardless of how the cyano group in fact interacts with the active site, empirical evidence at the time of the patent filing date at issue indicates that the group conveys an 8-fold boost in potency that would not have been ignored.

35. The Nichols Report also argues that “there is no teaching or suggestion in the CA ‘730 patent or the WO ‘496 publication to indicate that the order in which exemplified compounds are listed in a disclosure carries any significance.” (Nichols Report at ¶ 88.) According to Nichols, “assuming that a POSA had some familiarity reading patents, a POSA would likely know that the order of presentation of examples generally bears no correlation with compound desirability.” (*Id.*) I disagree. While I understand that there is no requirement for listing the order of compounds in a patent application or patent, it is my opinion and experience that the first compound listed usually does mean that the compound is a patent applicant’s lead compound. A typical and logical structure for a patent is to present the lead compound, its synthesis, and the properties of the lead and then discuss a multitude of minor derivatives of the lead.

36. Additionally, I note that the Nichols Report states that “Wiedeman recognized that Novo Nordisk and Boehringer Ingelheim ‘independently discovered this class of inhibitors.’ Yet, Wiedeman—highly skilled and above the level of a POSA discussing the art around the time of the invention without the benefit of hindsight—focused on **other compounds** from both references.” (Nichols Report at ¶ 119 (emphasis in original) (internal citations omitted).) Moreover, Dr. Nichols’s observation regarding Wiedeman identifying compound 30 as an attractive compound from WO ‘496 publication is erroneous. Wiedeman does not cite the WO ‘496 publication in reference to compound 30 (i.e., the compound 30 is not covered in WO ‘496 publication). In fact, Wiedeman in reference to compound 30 cites references cited as 132 and 41.

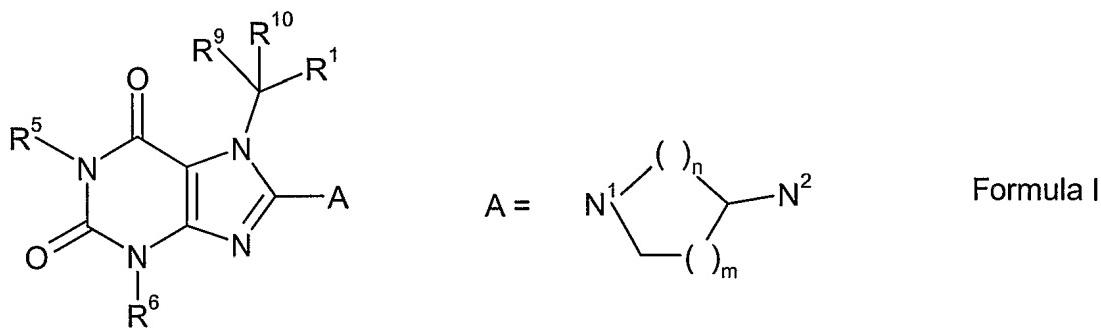
Citation 132 refers to WO 02002560 (see below):

132. Novo Nordisk A/S (Kanstrup AB, Christiansen LB, Lundbeck JM, Sams CK, Kristiansen M): Heterocyclic compounds, which are inhibitors of the enzyme DPP-IV. WO-02002560 (2002).

In fact, in reference to the WO 02002560 publication, Wiedeman expressly states that the claimed compounds in this application have the xanthine core with a pendant saturated cyclic diamine as depicted by compound 30 (Figure 5). Whereas, the compounds covered in WO '496 publication **do not** contain pendant saturated cyclic diamine group.

37. However, Wiedeman cites WO '496 publication at citation 134 indicating that ***Novo Nordisk also has an application specifying the pendant amines.*** The citation 134 refers to WO 03004496. Also, the abstract and the first paragraph of the heading “Description of Invention” discloses (in part as follows).

The present invention provides compounds of formula I



wherein A may be attached at either N¹ or at N² to the purine system and each n and m is one or two independently

Thus, no representative compound covered in WO '496 publication is disclosed in Wiedeman.

38. Further, it is my opinion that Wiedeman's discussion of other compounds, would not have discouraged a POSA from choosing DCAX upon reviewing both references.

Weideman's analysis was a landscape review of DPP-IV inhibitor classes at the time, with compounds discussed for a variety of reasons not necessarily related to their ultimate potential as pharmaceutical agents.⁹

B. The POSA Has The Necessary Crystal Structure To Render Alogliptin Obvious

39. Dr. Nichols also disagrees that it would have been obvious for a POSA to select DCAX as a lead compound primarily because there was no information on co-crystallization study of the non-peptide DPP-4 inhibitor/substrate complexed with the DPP-IV enzyme available at the time. Dr. Nichols acknowledges, however, that *DPP-IV enzyme crystal structure* discussed in the Structure References provide *some understanding* of molecular interactions of a peptidic substrate/inhibitor with residues present in the DPP-IV active sites.

40. For example, the Nichols Report states that a "POSA as of March 15, 2004, had no structure-based DPP-IV crystallographic information indicating that a cyano group attached to a phenyl (*e.g.*, a 2-cyanobenzyl group) in a non peptidic-type DPP-IV inhibitor behaved in any way like a cyano group attached to a pyrrolidine in a peptidic-type DPP-IV inhibitor." (Nichols Report at ¶ 103.) In my opinion, the absence of crystallographic information that Dr. Nichols so strongly relies upon would not preclude the POSA from recognizing the importance of that cyano group. In fact, it is reported in the art (*i.e.*, Fleming) that the nitrile group plays an important role as an electrophile/warhead that can bind to the serine hydroxyl group contained in the amino acids of the target enzyme (specifically serine proteases). Moreover, this group was so

⁹ Wiedeman made clear that their criteria for discussing example compounds was that they chose either one or more potent compounds as disclosed in the reference or one of the more completely characterized compounds as representatives of the series. For example, compound 30 was relatively poor DPP-IV inhibitor but had some pharmacokinetic data reported, which would explain Weideman's focus on that compound.

uniquely prevalent in DPP-IV inhibitors that it was hard to ignore; at the time, there were so few FDA approved drugs that incorporated a nitrile and so few serine protease inhibitors that utilized a nitrile as a warhead.¹⁰

41. Additionally, a POSA would have recognized that pyrrolidinyl or pyrrolidine based nitriles with primary amines were actually chemically unstable due to intramolecular cyclization and thus DCAX would be a more attractive lead than peptidic-like inhibitors.¹¹ Pyrrolidine nitriles cyclicize with the primary amine on the adjacent amino acid, thus “killing” two major pharmacophoric elements in peptidic like inhibitor compounds. A POSA would recognize that DCAX would not have this issue since it is physically impossible for the amine on the 3-aminopiperidinyl group to intramolecularly cyclize with the nitrile.

42. I also disagree with Dr. Nichols that a POSA would ignore the teachings from the Structure References because of their focus on *peptidic* substrate/inhibitor interactions. (See Nichols Report at ¶ 107.) In my opinion Dr. Nichols again takes a very narrow understanding of drug design methodology. The POSA does exactly this type of analysis in designing new drug candidates - they take known crystal structure information and known substrates and make logical, deductive decisions based on this information to identify new lead compound candidates to synthesize and test. I further note that the Structure References do not indicate or suggest that they will only help in the design of peptide-like inhibitors or discourage the use of their teachings in development of non-peptidic DPP-IV inhibitors. I thus maintain my opinion that a POSA would have believed it likely that similar binding principles would be involved with non-peptidic

¹⁰ See Fleming, F., et al., *Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore*, 53 J. Med. Chem. 7902-7912 (2010).

¹¹ See, i.e., Lambeir at 221, A., Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV, CRIT. REV. CLIN. LAB. SCI. 209-294 at 220, 222 (2003).

substrates, i.e., “(1) E205/E206 salt bridge interactions with an amine on the inhibitor; (2) the S1 hydrophobic pocket for binding the proline/substrate; (3) the S2 hydrophobic pocket; and (4) the active site serine S630.”

C. The POSA Would Have Modified The Scaffold Of The Lead Compound DCAX

43. In his report, Dr. Nichols further opines that the further modification of DCAX to alogliptin would not have been obvious. I disagree and discuss each of Dr. Nichols’ points below.

44. The Nichols Report states that “even assuming that a POSA would select DCAX as a lead compound from the many other, more ‘attractive’ choices, Dr. Ferraris fails to show that a POSA would have had a reason to modify the compound to make Alogliptin or Alogliptin benzoate with a reasonable expectation of success. All five of Dr. Ferraris’ selected ‘highly potent DPP-IV inhibitors’ in the CA ’730 patent contain a xanthine scaffold, a fact that Dr. Ferraris largely ignores in his search to find other ‘common structural features.’” (Nichols Report at ¶ 120.) I disagree. In my opinion a POSA would have recognized the relevance of the CA ’730 patent (and the WO ’496 publication) because each of these documents discloses compounds possessing DPP-IV inhibitory activity. I identified the five “highly potent DPP-IV inhibitors” based on their IC₅₀ values. I then discussed why the POSA would select DCAX and choose to scaffold hop, which was known at the time of the invention, to replace the xanthine with a uracil moiety. All indications in the prior art suggested the importance of the amino and cyano groups compared to the central core, i.e. the xanthine scaffold.¹²

¹² Dr. Nichols levels the same arguments against scaffold hopping against Dr. Rotella. Dr. Nichols states that “Dr. Rotella suggests that a POSA ‘would have been motived to optimize only the pyrimidinone core of the compound [of claim 162] *and maintain the rest of the compound.*’ Contrary to Dr. Rotella’s assertions,

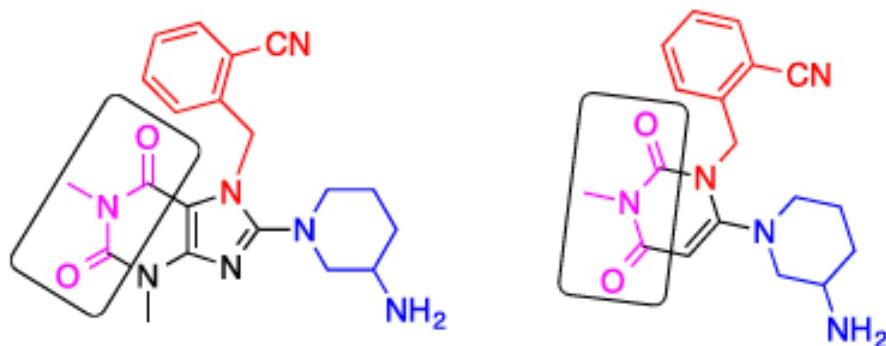
45. As additional support for his positions, Dr. Nichols states that “without the necessary relevant structural information in the context of designing non-peptidic-like DPP-IV inhibitors, a POSA would not have the necessary or properly informed ‘knowledge of the 3D structure of the [DPP-IV] enzyme/target’ to interpret ‘structure-activity relationships’ and apply it in using a structure-based drug design technique of ‘scaffold hopping’ with any reasonable expectation of success.” (Nichols Report at ¶ 123.) Again, I disagree with Dr. Nichols. Structure based drug design focused on non-peptidic inhibitors is not necessary for a POSA to consider and implement scaffold hopping. In fact, Dr. Nichols demonstrates this in his review of the pharmacophore of dopamine receptor agonists.¹³ In that paper published over a decade before 2004, Dr. Nichols and his co-authors highlight several active structures of dopamine receptor agonists all of which have a different central core. One has a seven membered ring with a nitrogen, two compounds have a six membered ring with an oxygen, one compound is bicyclic with a nitrogen, and another one has a six membered ring with a nitrogen. Dr. Nichols and his co-authors performed this analysis of the pharmacophore of the agonists without the aid of x-ray co-crystallography with the dopamine receptor.

46. The Nichols Report also states that “discarding the central framework upon which the drug molecule was built (here, the xanthine scaffold of Dr. Ferraris’ asserted lead compound DCAX), would lead to a complete disruption of the requisite 3-dimensional arrangement of the

and for reasons discussed in parts VII.A. and VII.B.1, instead of changing the central aspect of the compound, a POSA would much more readily first modify either the 2-cyanobenzyl group or the aminopiperidinyl group.” (Nichols Report at ¶ 305 (emphasis and edits in Nichols Report) (internal citations omitted).) I disagree with this statement. The cyano group and primary amino group were two distinctive hallmarks of DPP-IV inhibitors at the critical date for the patents-in-suit. The pyrimidinone core was not, and thus modifying the pyrimidinone would have been considered far less likely to be detrimental to the activity of DCAX.

¹³ Mottola et al., *Conformational Analysis of D1 Dopamine Receptor Agonists: Pharmacophore Assessment and Receptor Mapping*, 39 J. MED. CHEM. 285-296 (1992).

molecular components of the pharmacophore.” (Nichols Report at ¶ 137.) Again, I disagree. To illustrate this point, on the following structures, the benzonitrile group is attached to a nitrogen atom on the central ring in each compound (red in Figure below), the methyl group is also attached to a nitrogen atom sandwiched in between two carbonyl groups on the central ring (magenta in Figure below) in each compound, and the aminopiperidinyl group is attached to an alkene carbon adjacent to the cyanobenzyl group in each compound (blue in Figure below).



It is my opinion that replacing a xanthine with a uracil moiety thus will not result in a complete disruption of the 3-dimensional arrangement of the molecular components, a fact that a POSA also would have recognized at the time. Moreover, POSA would have knowledge available in art that the nitrogenous bases such as the purine bases (e.g. xanthine) and pyrimidine bases such as uracil are interchangeable.

47. The Nichols Report also tries to differentiate DCAZ and Alogliptin by noting that “the 2-cyanobenzyl and 3-aminopiperidinyl groups that Dr. Ferraris argues would be retained from DCAZ are located on the five-membered ring of the xanthine/purine bicyclic ring system. In contrast, these groups are located on Alogliptin’s six-membered monocyclic ring system.” (Nichols Report at ¶ 137.) Dr. Nichols ignores the *relative* positions in making this point. Each of these substituents (*i.e.*, the 2-cyanobenzyl and 3-aminopiperidinyl groups) is adjacent to each

other on both compounds - one on a nitrogen and one on a carbon, with a carbonyl on the next carbon over, then an N-methyl group on the next atom, followed by another carbonyl on the next atom. These are just a few of the several similarities between the two compounds.

48. The Nichols Report further states that uracil-based drugs are rare, citing the number of FDA approved drugs with that core. This position is irrelevant. The POSA would know that uracil is an RNA-base with a tremendous amount of chemistry surrounding it that would make it an attractive option.¹⁴

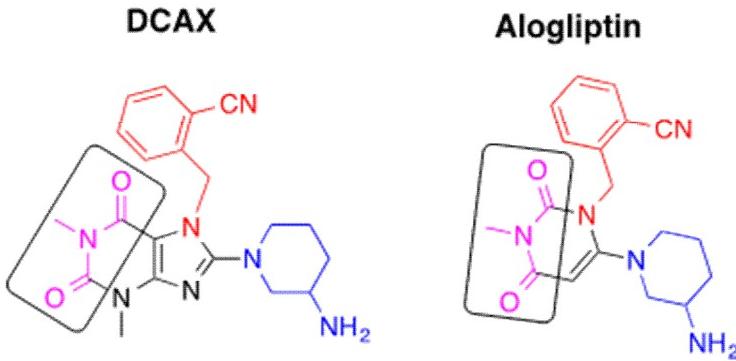
49. Dr. Nichols also states that “Dr. Ferraris argues that a POSA as of March 2004 would have been aware of ‘key structural components necessary’ from crystal structures of the DPP-IV enzyme ‘for DPP-IV inhibitors.’ First, even assuming that were true, such information would not tell a POSA how Alogliptin or DCAX would be bound within the DPP-IV enzyme.” (Nichols Report at ¶ 153.) Nichols continues that “even when the ‘structures and biological activities of ... target proteins have been well defined,’ it is still difficult for the industry to come up with good lead compounds.” (Nichols Report at ¶ 154.) Dr. Nichols again undercuts the common creativity that a POSA possesses. A medicinal chemist would hypothesize what structural components were necessary and do SAR the “old fashioned way”, i.e., using the structure activity data from what was known in the art, formulate a hypothesis outlining what parts of the molecule were the most relevant to activity and then proceed to systematically change the less critical component to develop a more promising candidate. A POSA would be able to come up with Alogliptin through a very straight forward and obvious route: 1) use DCAX as the lead; 2) keep the functional features or elements of this molecule that are likely most

¹⁴ Bardagi, J., et al., *Advances in the Synthesis of 5- and 6-Substituted Uracil Derivatives*, 479-514 (Nov. 20, 2009) (providing in-depth review of uracil chemistry.)

relevant to DPP-IV activity (cyanobenzyl group and amino piperidinyl group) by interacting with the active sites of the DPP-IV target; 3) exchange the central scaffold with a similar heterocycle.

50. The Nichols Report further states that “Dr. Ferraris asserts that Evans discloses that it is ‘essential’ to ‘include an N-terminal primary or secondary amine.’ (Ferraris at ¶ 139.) Citing Wiedeman, he further states that ‘[t]he majority of DPP-IV inhibitors under investigation as of March 2004 contained a primary or secondary amino group.’ (*Id.*) But that does not require the specific 3-aminopiperidinyl moiety of Alogliptin. Indeed, not one of Evans’ compounds contains the 3-aminopiperidinyl group, and only 1 of 33 compounds in Wiedeman does. In any event, Dr. Ferraris provides no evidence that a POSA would understand these disclosures to give motivation to retain the specific moiety found in Alogliptin while simultaneously altering the core of the compound.” (Nichols Report at ¶ 166.) It was obvious to the POSA to maintain the aminopiperidine moiety, however, because this moiety is present in ***all of the most potent inhibitors*** disclosed in the CA ’730 patent.

51. The Nichols Report also states that “Dr. Ferraris ignores that in his list of choices that a POSA must make to derive Alogliptin from DCAX. In addition, Alogliptin does not even have uracil as a base. It has N-methylated uracil. Dr. Ferraris does not try to justify that further change of N-methylating the uracil”. (Nichols Report at ¶ 167.) In my opinion the compounds (alogliptin and DCAX) are structurally similar, and the xanthine moiety is also methylated as illustrated in the below comparison:



52. Finally, I note that the Nichols Report states that “a POSA would not have been able to predict the properties of a molecule to which even small changes had been made. *A fortiori*, a POSA would have no reasonable ability to predict the properties of a compound like Alogliptin resulting from Dr. Ferraris’ asserted dramatic structural modifications of DCAX.” (Nichols Report at ¶ 169.) I disagree. Making structural modification to a compound that has known DPP-IV inhibitory activity is well within the purview of the POSA, and the POSA would expect the modified compound to also exhibit DPP-IV inhibitory activity. I do not consider such modifications dramatic at all.

D. The POSA Would Understand How To Resolve Enantiomers And Expect One To Be More Active As Well As Determine And Identify Appropriate Salts

53. In discussing his opinions on certain claims of the patents-in-suit relating to enantiomers, Dr. Nichols has taken the untenable position that “although a POSA would know to resolve the enantiomers, the POSA would not be able to predict which one was more potent. Moreover, as discussed in part VII.A. of this report, there would have been no such expectation of success as it is difficult to predict whether a new chemical compound will have particular pharmacological properties, even when analogous compounds may be known to the POSA”. (Nichols Report at ¶ 178.) The POSA is not expected to guess beforehand which enantiomer will have the better properties, however. The POSA would merely make and then examine the

two enantiomers empirically. The investigation of enantiomers and their properties was routine practice in 2004, driven by the common knowledge that enantiomers may have different activities and/or result in different side effects that should be investigated prior to FDA submission.¹⁵

54. In a similar vein, the Nichols Report states that “a POSA would, without any justification, be further required to choose a specific enantiomer of the 3-aminopiperidinyl group on the resulting new pharmacophore.” (Nichols Report at ¶ 181.) In my opinion, the POSA would not have to choose without any justification or routine experimentation. There are only two options, and the POSA would know that one enantiomer or the other may be more active once they were made and tested.

55. I further disagree with Dr. Nichols in his opinion relating to claims to salts, including the benzoate salt. Nichols states that “a POSA would have no reasonable ability to predict the pharmacological properties or safety profile of a compound like the benzoate salt of Alogliptin resulting from each of Dr. Ferraris’ asserted selections in modifying DCAX. In my opinion, not only does Dr. Ferraris’ POSA lack the necessary motivation to make each and every one of these choices, Dr. Ferraris’ POSA also has no reasonable expectation of success given the countless number of possible results following each and every one of these choices.” (Nichols Report at ¶ 193.) A benzoate salt is an obvious choice to a POSA because such salts would be on any POSA’s “salt panel.” At the time in question (and for decades before), salts were known in drug discovery to improve the pharmaceutical properties of the compound (e.g. solubility, crystallinity, chemical stability being the most common properties affected). To maximize the potential of lead compounds, it was standard practice to make many salt forms for testing and

¹⁵ I further note that the WO '496 publication disclosed an R-isomer of DCAX as an HCl salt as Example 16, which is the same isomer identified as best for alogliptin.

evaluation. It further is easy to make salts of many of the most common acids when the compound have an amine, which Alogliptin does. The salt panel, i.e., the routine salts that would be developed and tested for a lead like alogliptin would almost certainly include many of the most common organic acids such as acetic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid and inorganic salts as well such as HCl, HBr, H₂SO₄, H₃PO₄, and dozens of others. This would be routine and expected experimentation for a POSA.

V. CONCLUSION

56. For the reasons explained in this report, it is my opinion that one of ordinary skill in the art in March 2004 would have considered the asserted claims invalid as obvious over the combinations of references set forth above.

Signed this 23rd day of August 2019



Dana Ferraris, Ph.D., M.B.A.

EXHIBIT A**MATERIALS CONSIDERED**

Description	Document Production Range
U.S. Patent No. 7,807,689	
U.S. Patent No. 8,288,539	
U.S. Patent No. 8,176,663	
File History of Patent No. 7,807,689 & References	
File History of Patent No. 8,288,539 & References	
File History of Patent No. 8,176,663 & References	
U.S. Patent No. 5,142,051 to Holy et al., <i>N-Phosphonylmethoxyalkyl Derivatives of Pyrimidine and Purine Bases and a Therapeutical Composition Therefrom with Antiviral Activity</i> , issued Aug. 25, 1992	IndAlo0000990- IndAlo0000996
U.S. Patent No. 5,780,476 to Underiner et al., <i>Hydroxyl-Containing Xanthine Compounds</i> , issued July 14, 1998	IndAlo0000997- IndAlo0001036
U.S. Patent No. 6,699,871 to Edmondson et al., <i>Beta-Amino Heterocyclic Dipeptidyl Peptidase Inhibitors for the Treatment or Prevention of Diabetes</i> , issued March 2, 2004	IndAlo0079268- IndAlo0079290
Canadian Patent No. CA 2 435 730, <i>Xanthine Derivatives, The Preparation Thereof and Their Use As Pharmaceutical Compositions</i> , published Jan. 16, 2003	IndAlo0000374- IndAlo0000737
Canadian Patent No. CA 2 496 249 to Himmelsbach et al., <i>8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments</i> , published on March 4, 2004	IndAlo0045116- IndAlo0045335
International Publication WO 03/004496 to Kanstrup et al., <i>DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes</i> , published Jan. 16, 2003	IndAlo0000738- IndAlo0000839
International Publication WO 2003/004498 to Edmonson, <i>Beta-amino Tetrahydroimidazo (1, 2-a) Pyrazines And Tetrahydrotriazolo (4, 3-a) Pyrazines As Dipeptidyl</i>	IndAlo0079291- IndAlo0079359

<i>Peptidase Inhibitors For The Treatment Or Prevention Of Diabetes</i> , published Jan. 16, 2003	
International Publication WO 2002/068420 A1, <i>Xanthine Derivatives, Production and Use Thereof As Medicament</i> , filed Feb. 21, 2002 and published Sept. 6, 2002	IndAlo0000001- IndAlo0000373
Aertgeerts, K., et al., <i>Crystal structure of human dipeptidyl peptidase IV in complex with a decapeptide reveals details on substrate specificity and tetrahedral intermediate formulation</i> , 13(2) Protein Sci. 412-421 (Feb. 2004)	IndAlo0000952- IndAlo0000963
Ahrén, B. et al., <i>Inhibition Of Dipeptidyl Peptidase IV Improves Metabolic Control Over A 4-Week Study Period In Type 2 Diabetes</i> , 25(5) Diabetes Care 869-875 (May 2002)	IndAlo0079111- IndAlo0079117
Anderson, A., <i>The Process of Structure-Based Drug Design</i> , 10(9) Chem. & Bio. 787-797 (Sept. 2003)	IndAlo0000966- IndAlo0000976
Berge, S., et al., <i>Pharmaceutical Salts</i> , 66(1) J. Pharm. Sci., 1-19 (Jan. 1977)	IndAlo0044978- IndAlo0044996
Böhm, H. et al., <i>Scaffold Hopping</i> , 1(3) Drug Discovery Today: Technologies 217-223 (Dec. 2004)	IndAlo0079118- IndAlo0079125
Campbell, D.B., <i>Stereoselectivity in Clinical Pharmacokinetics and Drug Development</i> , 15(2) Euro. J. Drug Metabolism & Pharmacokinetics, 109-125 (April 1990)	IndAlo0045336- IndAlo0045354
Crossley, R., <i>Chirality and the Biological Activity of Drugs</i> , CRC Press (1995)	IndAlo0045355- IndAlo0045378
Davies, T.G., et al., <i>Structure-based design of cyclin-dependent kinase inhibitors</i> , 93(2-3) Pharm. & Therapeutics 125-133 (Feb.-Mar. 2002)	IndAlo0001037- IndAlo0001045
Engel, M., et al., <i>The Crystal Structure Of Dipeptidyl Peptidase IV (CD26) Reveals Its Functional Regulation And Enzymatic Mechanism</i> , 100(9) PNAS 5063-068 (Apr. 29, 2003)	IndAlo0000946- IndAlo0000951
Evans, D., <i>Dipeptidyl Peptidase IV Inhibitors</i> , 5(6) IDrugs 577-585 (Jun. 2002)	IndAlo0000840- IndAlo0000848
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EXHIBIT 13

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

TORRENT PHARMACEUTICALS LIMITED and TORRENT PHARMA INC.,

Defendants/Counterclaim-
Plaintiffs.

Civil Action No. 17-3186-SRC-CLW

(CONSOLIDATED)

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

INDOCO REMEDIES LTD.,

Defendant/Counterclaim-
Plaintiff.

Civil Action No. 17-7301-SRC-CLW

**OPENING EXPERT REPORT OF DAVID P. ROTELLA, PH.D.
REGARDING THE INVALIDITY OF U.S. PATENT NO. 7,807,689**

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I. INTRODUCTION

1. I have been retained by the law firm Pillsbury Winthrop Shaw Pittman LLP (“Pillsbury”) on behalf of Defendants Torrent Pharmaceuticals Limited and Torrent Pharma Inc. (collectively “Torrent”) and also on behalf of Indoco Remedies Ltd. (“Indoco”) by the law firm of Seyfarth Shaw LLP to serve as a consultant and expert witness in connection with the above-captioned action matter. I submit this expert report (“Report”) pursuant to Federal Rule of Civil Procedure 26(a)(2)(B).

2. I am being compensated for the time I spend working on this matter. My compensation on this matter is \$450 per hour.¹ I have no financial interests in any of the parties to this dispute. I receive no other compensation from the parties nor will I receive any additional compensation based on either the nature of my opinions or the outcome in this matter.

3. I have been advised that claims 1, 3, 4, 9, 11-12, 43, and 49 of U.S. Patent No. 7,807,689 (“the ’689 patent”) have been asserted against Torrent and Indoco in this case. I have examined the ’689 patent and the asserted claims. This Report offers, among other things, my opinions relating to issues regarding the invalidity of the asserted claims of the ’689 patent including the basis and reasons in support of those opinions.

4. The opinions set forth in this Report are based on my knowledge and understanding acquired during both the course of my formal education and my extensive drug discovery and medicinal chemistry experience extending over the past 30 years. In connection with preparing this Report, I have also reviewed and considered the list of materials attached as Exhibit A, including the ’689 patent and portions of its prosecution history, and various other

¹ I am being billed at a rate of \$600 per hour but only receiving \$450 as compensation because a portion goes to an expert retention service.

materials. As this litigation progresses, I understand that I may be asked to review additional materials. I reserve the right to amend, supplement or clarify my opinions including the list of materials in Exhibit A as needed.

II. QUALIFICATIONS AND EXPERIENCE

A. Education and Training

5. I received my Ph.D. in Medicinal Chemistry from The Ohio State University in 1985 and my B.S. Pharm. from the University of Pittsburgh in 1981. I was a Postdoctoral Scholar in the Department of Chemistry at The Pennsylvania State University from 1985 to 1987.

6. I am currently the Margaret and Herman Sokol Professor of Chemistry in the Department of Chemistry and Biochemistry and in the Sokol Institute of Pharmaceutical Life Sciences at Montclair State University. I have been a member of the faculty of this university since 2011.

7. I am also currently an adjunct professor in the Department of Pharmaceutical Sciences at the University of Pittsburgh, in the Center for Drug Discovery at Northeastern University, and in the Department of Medicinal Chemistry at the University of Mississippi. I have been a member of the faculty of these departments since 2010, 2010, and 2009, respectively.

8. Prior to my university professorships, I was a research scientist at multiple pharmaceutical companies including at Bristol-Myers Squibb PRI, Lexicon Pharmaceuticals, and Wyeth Research/Pfizer. During this time, from 1991-2010, my industry experience focused on drug discovery and development. I have successfully developed novel phosphodiesterase type-5 inhibitors with better in vitro potency and selectivity as compared to existing drug sildenafil. I

have also been involved in developing other types of drugs, including DPP-IV inhibitors and PDE5 inhibitor.

9. My current research focuses on protein kinase inhibitors for anti-infective and anti-inflammatory applications. Specifically, I work on the discovery of new agents useful for the potential treatment of parasitic and neurodegenerative diseases, including the synthesizing of new analogs of a lead structure as potential protein kinase inhibitors and investigation of structure-activity relationships in a product that has HSP90 inhibitor activity.

10. I have authored or co-authored more than 20 abstracts for presentation at professional meetings, over 40 peer-reviewed journal articles, and seven book chapters, including publications in the areas of dipeptidyl peptidase-IV (DPP-IV) inhibitors and treatment of Type 2 diabetes. I have also edited or co-edited five books in the field of Medicinal Chemistry. I have received numerous honors, fellowships and awards, and am an inventor or co-inventor on seven granted patents.

11. A summary of my education, experience, publications, awards and honors, patents, publications, and presentations is provided in my CV, a copy of which is attached herein as Exhibit B.

B. Prior Testimony

12. In the last four years, I have testified as an expert either at trial or by deposition in the following matters:

- a. *AstraZeneca AB v. Mylan Pharmaceuticals Inc.*, No. 14-cv-664 (consolidated) (D. Del. 2014-2017);
- b. *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, IPR2015-01340 (PTAB 2015-2017);
- c. *Gilead Sciences Inc. et al v. AbbVie Inc.*, No. 13-cv-02034 (D. Del. 2013-2016);
- d. *Takeda GMBH et al. v. Mylan Pharmaceuticals Inc.*, No. 15-cv-03375

(consolidated) (D.N.J. 2015-2018); and

e. *Erfindergemeinschaft UroPep GbR v. Eli Lilly and Co. et al.*, No. 15-cv-1202 (E.D. Tex. 2015-2017).

III. SUMMARY OF OPINIONS

13. It is my opinion that each asserted claim of the '689 patent is invalid for obviousness-type double patenting over claim 162 of U.S. Patent No. 7,723,344 (the "Feng patent") because each asserted claim of the '689 patent is not patentably distinct from claim 162 of the Feng patent.

IV. THE STATE OF THE ART AT THE TIME OF THE ALLEGED INVENTION

14. Below I describe the details of what was generally known in the art as of November 2004, including: (i) type 2 diabetes mellitus and some of known anti-diabetic agents; (ii) the crystal structures of DPP-IV with small molecule inhibitors, and the structures of several known DPP-IV inhibitors and their use in treatment of Type 2 diabetes mellitus; (iii) common strategies such as structure-based drug design approach, including scaffold replacement and fragment-based screening approaches, employed by medicinal chemists to aid in discovering and developing novel potent compounds that have improved properties.

15. Type 2 diabetes mellitus is a disease that results in too much sugar in the blood, *i.e.*, high blood glucose. Prior to 2004, there were various known diabetes treatments with different underlying action mechanisms. For example, antiabsorptives (such as miglitol) reduce the quantity of glucose entering the bloodstream from the intestinal tract; insulin secretagogues (such as Daonil®) stimulate the secretion from pancreatic β-cells; insulin sensitizers (such as metformin) improve insulin resistance; incretin mimetics (also known as GLP-1 receptor agonists) active the glucagon-like peptide 1 (GLP-1) receptor; and dipeptidyl peptidase-IV inhibitors inhibit the breakdown of GLP-1.

16. Dipeptidyl peptidase-IV (DPP-IV), also known as CD26, is a serine protease belonging to the group of post-proline/alanine cleaving amino-dipeptidases, which specifically removes the two N-terminal amino acids from proteins having proline or alanine. (See WO 03/004496 to Kanstrup *et al.*, “DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes,” published January 16, 2003 (“Kanstrup 2003”) at 2.) As a dipeptidyl peptidase, DPP-IV plays a major role in the regulation of many physiological processes.

17. For example, DPP-IV has a major role in maintaining glucose homeostasis because its substrates include the incretin hormone glucagon-like peptide 1 (GLP-1). GLP-1 functions as a mediator of glucose-stimulated insulin secretion, thus, GLP-1 based therapies were investigated primarily for treatment of non-insulin-dependent diabetes mellitus (Type 2 diabetes). GLP-1 is only active in its intact form. Inhibition of DPP-IV leads to increased levels of active (intact form) GLP-1 in the circulation, enhanced insulin secretion and improved glucose tolerance. As a result, DPP-IV inhibitors have been investigated for the treatment of patients with Type-2 diabetes mellitus, a disease characterized by decreased glucose tolerance. (Kanstrup 2003 at 2; Evans, M.E., “Dipeptidyl peptidase IV inhibitors,” IDrugs 5(6):577-585 (June 2002) (“Evans”), at 579.)

18. Since the early 1980s, structure-based drug design had been commonly used to develop inhibitors that lead to therapeutic drugs. (See Anderson, A.C., “The Process of Structure-Based Drug Design,” CHEM & BIO 10:787-797 (Sept. 2003) (“Anderson”) at 790-91). Under the structure-based drug design approach, modifications to a candidate molecule for a novel potent inhibitor are designed based on hypotheses arising from the structural information on the enzyme-inhibitor and/or enzyme-substrate complexes, including, for example, interactions of the substrate with the target site (catalytic site or active site) of the enzyme/protein, which

were usually disclosed in the co-crystallization studies where the enzyme/protein is crystallized with an initial substrate. (*Id.* at 790). On an atomic level, such interactions between protein and ligands can roughly be understood in terms of hydrogen bonding, hydrophobic interactions, and/or other noncovalent interactions such as $\pi-\pi$ stacking (also known as pi stacking, i.e., the noncovalent interactions between aromatic rings). (*Id.*; see also McGaughey, Georgia B., et al., “ π -Stacking Interactions,” *The Journal of Biological Chemistry*, Vol. 273, No. 25, Issue of June 19, pp. 15458–15463 (1998) (“McGaughey 1998”), at 15458).

19. At the time of invention, it was not uncommon in drug discovery that researchers replace the core fragment, also called the scaffold, of a molecule with an interesting biological activity with another scaffold having a different chemical structure but similar features that would allow the new molecule to interact in a similar way with the target protein as the original molecule. (See Bohm et al., “Scaffold hopping,” *Drug Discovery Today: Technologies* 2004, 1(3):217-223 (“Bohm 2004”)),² at 217-218). Scaffold replacement was one of the known structure-based approaches used to discover novel compounds. (*Id.* at 217). At the time of the alleged invention that is the subject of the ’689 patent, computational tools were commonly employed that would use the known crystal structure of a target protein (such as DPP-IV) to search for the right structure fragment to modify the scaffold of existing inhibitors and thus design a novel scaffold (*Id.* at 222-223). For example, scaffold replacement could entail replacement of the original scaffold with a fragment found from searching an appropriate predefined database of fragments that would then return matching 3-D structures that can be used

² While Bohm 2004 was published in December 2004—prior to the priority date of the ’689 patent—and thus is not statutory prior art, it reflects and provides evidence of knowledge of one of ordinary skill in the art because it relies on and reviews successful examples of scaffold hopping occurred prior to March 2004. (See Bohm 2004 at 217-218, 222).

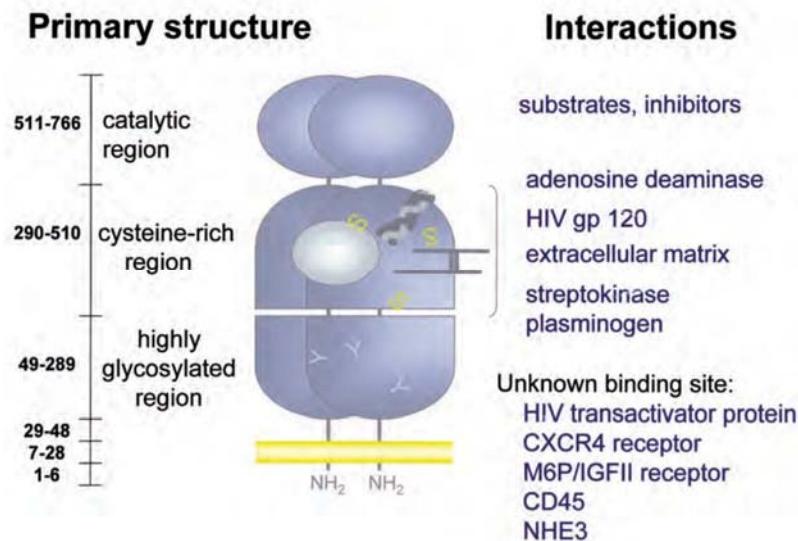
to potentially replace the original scaffold. (*Id.*) Fragment databases (known also as “fragment screening libraries”) usually contain a collection of compounds that have been reported in the literature.

20. A person of ordinary skill in the art (“POSA”) would have been motivated to use scaffold replacement approach develop novel compounds for several reasons known in the art: 1) it was known that a change in the central scaffold can lead to a novel structure including one that is patentable, particularly when the starting small molecules have been disclosed; 2) a replacement of the scaffold may lead to an improved binding affinity as well as improved overall drug metabolism and pharmacokinetics properties; and 3) a replacement in the scaffold may be able to improve the solubility of a compound. (*Id.* at 218).

21. Prior to 2004, scaffold replacement had been used successfully in many important new drug discoveries, particularly when researchers were looking to develop non-peptidic small molecules rather than peptidic molecules. (*Id.* at 218). The scaffold replacement approach was based on the observations that structurally different molecules can bind to the same target if such structures maintain some essential features of the template, i.e., an existing compound displaying the desired biological activity (in this case, a known DPP-IV inhibitor). (*Id.* at 217). Scaffold replacement attempts to maintain as needed the essential features of the template through an examination of the key interactions with its binding site on the target protein. The goal is to preserve or improve on the molecular recognition between the target protein enzyme and inhibitor. Scaffold replacement thus takes advantage of the available crystal structures of protein-inhibitor or enzyme-substrate complexes. (*Id.* at 222).

22. Prior to 2004, the crystal structures of human DPP-IV as well as its co-crystallization with various inhibitors and substrates were well known in the art. For example,

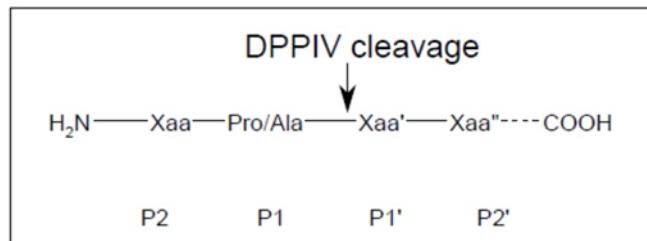
both Aertgeerts, K., et al., Crystal structure of human dipeptidyl peptidase IV in complex with a decapeptide reveals details on substrate specificity and tetrahedral intermediate formation, 13(2) PROTEIN SCI. 412-421 (Feb. 2004) (“Aertgeerts”), and Engel, M., et al., The crystal structure of dipeptidyl peptidase IV (CD26) reveals its functional regulation and enzymatic mechanism, 100(9) PNAS 5063-5068 (Apr. 29, 2003) (“Engel”) describe the crystal structures of DPP-IV and the structure features that underlie the substrate/inhibitor recognition and their interaction with DPP-IV. Lambeir A.M., et al., “Dipeptidyl-Peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV,” Crit. Rev. Clin. Lab. Sci. 40: 209–294 (2003) (“Lambeir”) reviews and summarizes the structure properties of DPP-IV and its interactions with inhibitors. (See Lambeir at Plates 1 and 2; & 220-223)



23. DPP-IV is a serine protease that cleaves preferentially Xaa-Pro (Xaa represents any amino acid), and to a lesser extent, Xaa-Ala dipeptides on the N-terminal end of oligopeptides with typical length of 30 aa. The P1, P2 positions³ are depicted schematically

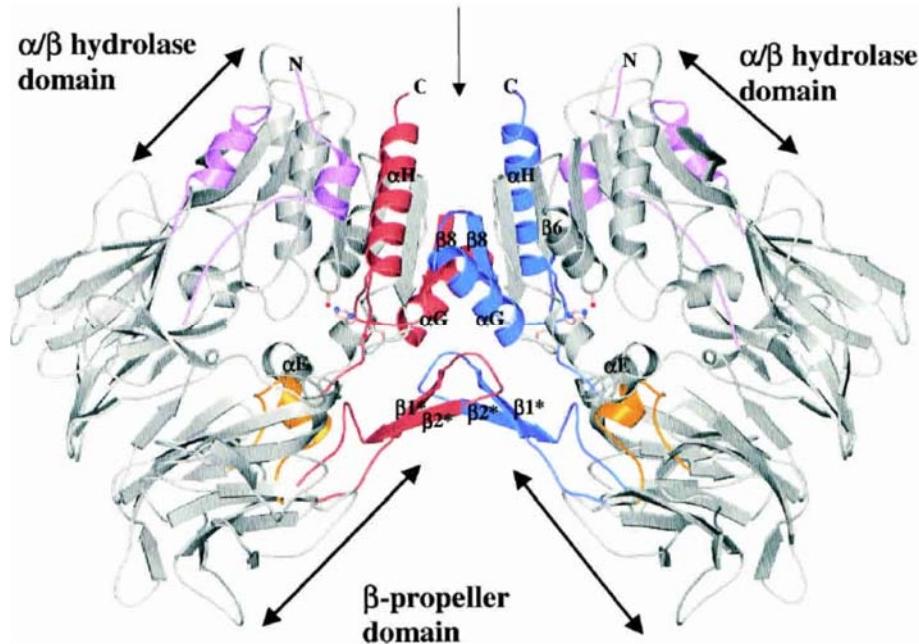
³ Under the common nomenclature, residues in a peptide substrate are called P1, P2, and P1', P2',

below. (*See* Wiedeman, P.E. & Trevillyan, J.M., Dipeptidyl peptidase IV inhibitors for the treatment of impaired glucose tolerance and type 2 diabetes, 4(4) Current Opinion in Investigational Drugs 412-420 (Apr. 2003) (“Wiedeman”) at 413-14). The Corresponding binding subsites on the enzyme (DPP-IV) are called S1, S2 and S1’, S2’... Sn’. (Lambeir at 216.)



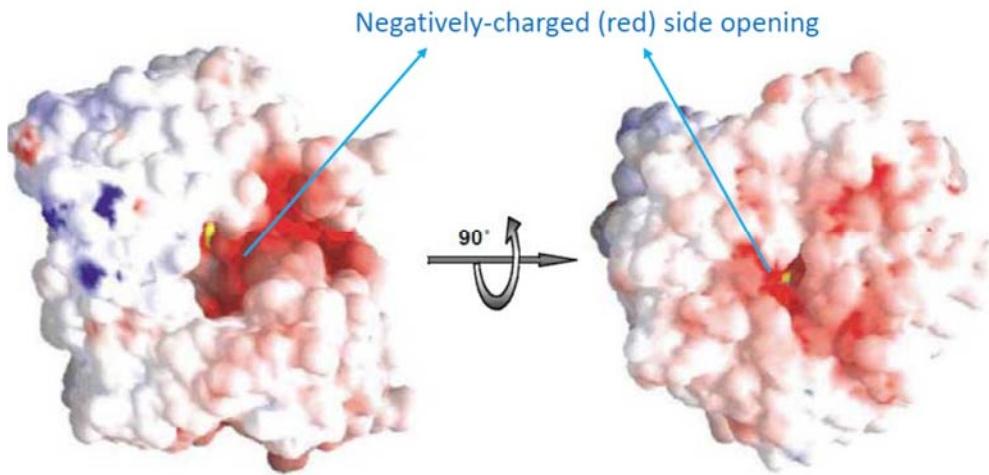
24. The biologically active form of DPP-IV exists as a dimer comprising two domains: an α/β hydrolase domain and an eight-bladed propeller domain (shown in the ribbon diagram below). (Aertgeerts at 413-414, Figure 1). Two openings provide access to the cavity of DPP-IV: a funnel shaped opening through the β -propeller and a larger opening between the hydrolase and propeller domains.

P3'...Pn' counting from the scissile bond toward the N- and C- terminus of the peptide, respectively. (*See* Lambeir at 216).



25. Both openings are negatively charged (as illustrated in the figure⁴ below), which attracts the positively charged amine found in *all* known DPP-IV inhibitors. (Wiedeman at 418). It was known in the art that the substrate may access the DPP-IV via a side opening formed at the interface of the β-propeller and hydrolase domains. (Aertgeerts at 414).

⁴ In this figure, the surface of a DPP-IV molecule (not the dimer) is colored based on the surfaces' electrostatic potential. The negatively charged surface is red and positively charged surface is blue, viewed from the side and the bottom of the β-propeller. The yellow is a DPP-IV inhibitor (Val-Pyr).



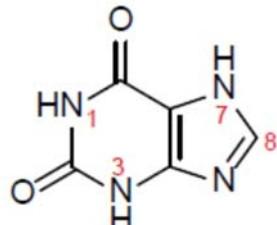
26. The crystal structures in the prior art disclose that there is a detailed understanding in the prior art of the molecular mechanisms that determine the interactions of the substrate with the residues present at the active site of DPP-IV. First, two essential glutamic acid residues, E205 and E206, form a salt bridge (a combination of two noncovalent interactions: hydrogen bonding and ionic bonding) to an amine group in the inhibitor, and this interaction is responsible for orienting the peptide/substrate for cleavage. (Wiedeman at 418; Aertgeerts at 415). Second, a well-defined hydrophobic pocket forms the S1 binding site for proline/substrate recognition and determines the binding specificity of the substrate. The hydrophobic S1 pocket is lined by residues Val 656, Tyr 631, Tyr 662, Trp 659, Tyr 666, and Val 711. Third, the S2 pocket is hydrophobic and is composed of the side chains of Arg 125, Phe 357, Tyr 547, Pro 550, Tyr 631, and Tyr 666. Other binding sites (such as the S1', S2' binding sites) are less well defined.

27. Another essential element for DPP-IV activity is Ser 630, which is located on the “nucleophilic elbow” formed by residues Gly-Trp-Ser630-Tyr-Gly. The hydroxyl group of the serine residue (S630) moves significantly to optimally interact with the scissile carbonyl bond of the peptide when binding to the substrate. (Aertgeerts at 416). This hydroxyl group was also

known to interact with certain functional groups (e.g., cyano, boronic acid) found in certain classes of DPP-IV inhibitors. (*See* Evans at 578).

28. DPP-IV inhibitors can be classified into two main categories, namely dipeptide-like and non-peptidic inhibitors. (Evans at 579; Wiedeman at 417). Dipeptide-like inhibitors are inhibitors that mimic to some extent the structure of the preferred substrates. Because the pyrrolidine ring of proline provides a strong recognition element for DPP-IV substrate, many of the dipeptide-like inhibitors incorporate a pyrrolidine ring. (Wiedeman at 414). Among the dipeptide-like inhibitors, 2-cyanopyrrole was reported as an important structural element that contributes to the potency of DPP-IV inhibitors because the cyano group at the 2-position on the pyrrolidine acts as “a serine ‘hook’ forming an imidate with the catalytic-site serine” (i.e., S360). (*Id.*)

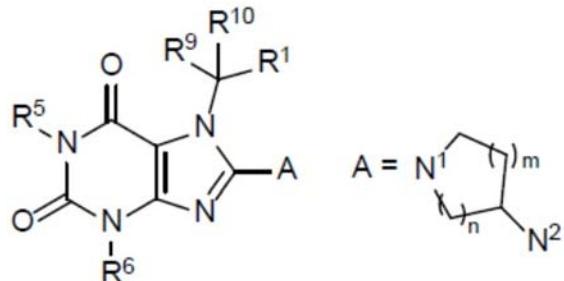
29. Among the non-peptidic class of DPP-IV inhibitors, the compounds having xanthine core (structure shown below), discovered by two companies (Novo Nordisk and Boehringer Ingelheim) independently, were found to be of interest. (Wiedeman at 417.)



xanthine

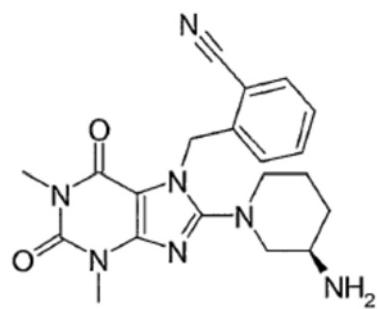
30. For example, Kanstrup 2003, filed by Novo Nordisk, discloses xanthine-based non-peptidic DPP-IV inhibitors with the general structure of Formula I below. (Kanstrup 2003 at Abstract). Specifically, Kanstrup 2003 discloses that xanthine derivatives with a cyclic

diamine attached at either one of the amino groups of the diamine to position 8 of the purine skeleton are “potent and selective inhibitors of DPP-IV” and can be used for treatment of Type 2 diabetes. (*Id.* at 2, ll. 23-29; at 8, ll. 1-3).



Formula I

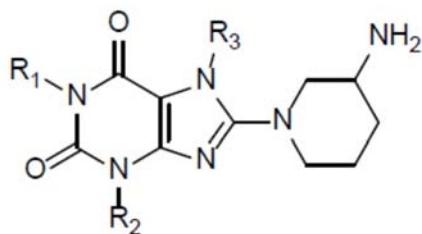
31. Notably, many of the working examples from Kanstrup 2003 teach DPP-IV inhibitors having 3-aminopiperidinyl group attached to position 8, with R-enantiomer at the amino group as the preferred configuration at the amino group. Notably, Example 16 of Kanstrup 2003, containing adjacent 2-cyanobenzyl and aminopiperidinyl groups, as illustrated in the following formula structure:



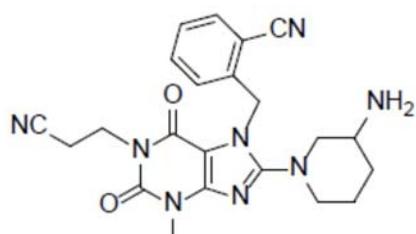
Example 16 of Kanstrup 2003

32. Shortly after Kanstrup 2003’s disclosure, C.A. Patent No. 2,496,249 to Himmelsbach et al., entitled “8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments,” published on March 4, 2004 (“Mark 2004”), filed

independently by Boehringer Ingelheim, also disclosed various xanthine-based DPP-IV inhibitors with a 3-aminopiperidinyl group attached to position 8 of the xanthine core (as shown in Formula I below). (Mark 2004 at Abstract). Mark 2004 discloses that many of these compounds exhibit high potency in inhibiting DPP-IV activity expressed as IC₅₀ values ranging from 1 nM to 10 nM. (*Id.* at 33-35).

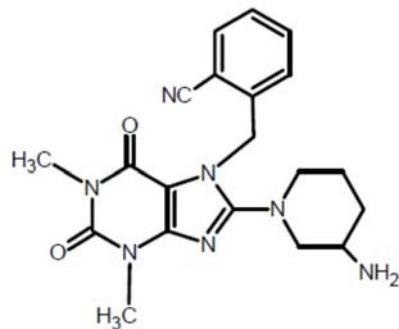


33. Mark 2004 also discloses various xanthine-based compounds with both a cyano group (2-cyanobenzyl at position 7 of the xanthine ring) and 3-aminopiperidinyl group at position 8. (*Id.* at pp. 135-185, Compounds (Example Nos. 1(1), 1(121), 2(4), 2(9), 2(10), 2(11), 2(12), 2(14), 2(17), 2(90), 2(115), and 2(263))). For example, Compound 1(1) has the following formula structure:



34. While Mark 2004 does not disclose the exact inhibition potency of these compounds containing both 2-cyanobenzyl and 3-aminopiperidinyl groups, the same research group from Boehringer Ingelheim reported in a separate reference the potency (IC₅₀) of

compound **1(121)** (1,3-dimethyl-7-(2-cyanobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine with both 2-cyanobenzyl and 3-aminopiperidinyl groups (structure shown as below) is 10 nM. (See C.A. Patent No. 2,435,730 to Himmelsbach et al., entitled “xanthines derivatives, the production thereof and their use as pharmaceutical compositions,” published on September 6, 2002 (“CA ’730”), at 99, 197).



Compound 1(121)

35. Thus, the state of the art at the time of the alleged invention had revealed that both the cyano group (as the 2-cyanobenzyl) and 3-aminopiperidinyl group are important structure elements in this group of molecules, which lead to great potency and selectivity as DPP-IV inhibitors.

36. There are at least two common resources for a POSA to rely on as a starting point for the drug discovery of new DPP-IV inhibitors for use for the treatment of diabetes: known molecules that are known to have inhibiting activity of DPP-IV, and biologically active natural products found for example in plants. Prior to 2004, there were many examples of new drugs developed from plant sources, for example, immunosuppressants for organ transplants (e.g., cyclosporine, rapamycins), and anticancer drugs (e.g., paclitaxel, vincristine, and vinblastine).

37. Kim et al., “Anti-diabetic Activity of Constituents of Lycii Fructus,” The Journal

of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) (“Kim 1998”) was one such reference that is available to a POSA. Kim 1998 describes the anti-diabetic activity observed in constituents of a fruit, Lycii Fructus, which was a common ingredient used in food preparation and also traditional oriental medicine to treat diabetes, fever and other diseases etc. (Kim 1998 at 378).

38. Kim 1998 discloses that due to safety concern and side effects in current diabetes treatments, they “conducted the present study [on Lycii Fructus] in order to develop safer hypoglycemic agents from herbal medicines that are more commonly used as folk remedies for diabetes.” (*Id.*) Kim 1998 describes the results of the study in which the anti-diabetic effects of four constituents of Lycii Fructus (uracil, rutin, betaine, and ascorbic acid), along with commercially available anti-diabetic medication Daonil® (glibenclamide)), were tested on streptozotocin-induced diabetic rats. (*Id.* at 381). Kim 1998 reports blood glucose lowering effects by three of the isolated Lycii Fructus substances: 18.3% for Uracil (2,4(1H,3H)-Pyrimidinedione), 19.9% for Rutin (3, 3’, 4’, 5, 7-pentahydroxyflavone-3-rutinoside), and 18.1% for Ascorbic Acid. (*Id.* at Table 1 reproduced below). In this model Daonil® reduced blood glucose by 12.6%. The chemical structures of Uracil, Rutin and ascorbic acid are also shown below:

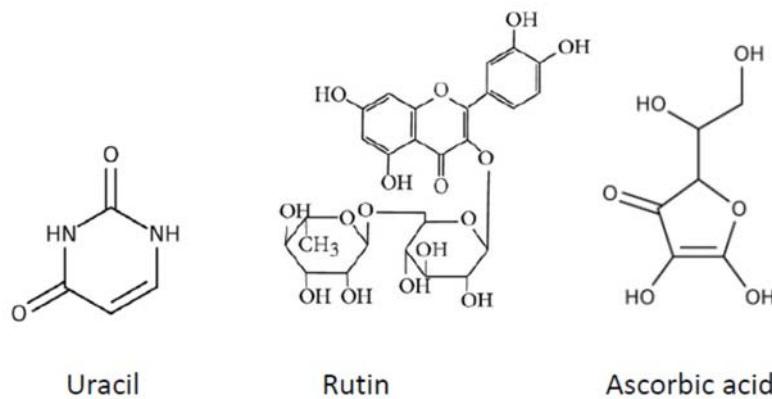


Table I. Effect of some constituents on blood glucose level in diabetic rats

Group	Dose (mg/kg p.o.)	No. of animal	blood glucose 0 day	level (mg/dl) 7 days	Blood glucose Inhibition rate (%)
Control	-	11	521.9±54.8	527.3±31.9	
Uracil	45	7	535.5±55.3	437.6±37.5*	18.3
Rutin	180	6	513.0±45.1	411.1±78.4*	19.9
Betaine	45	7	517.4±63.1	488.6±36.4	5.6
Ascorbic Acid	45	7	545.6±67.6	447.0±64.8*	18.1
Daonil®	5	7	545.9±40.1	477.0±36.3	12.6

Values are mean±S.D., Significantly different from the control (*p<0.05). [§]Commercial drug.

39. Kim 1998 also reports that unlike rutin and ascorbic acid which had been previously reported in the art to have antidiabetic activity, this was the first time that uracil was reported to have anti-diabetic effects. (*Id.* at 382.) Kim 1998 concluded that uracil “demonstrate[d] significant anti-diabetic effects, suggesting [its] potential [use] as [a] new diabetes treatment.” (*Id.*)

V. PROSECUTION HISTORY OF THE '698 PATENT

A. Overview of The '689 patent

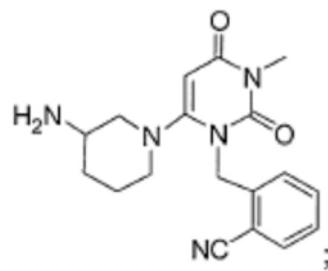
40. The '689 patent is entitled “Dipeptidyl Peptidase Inhibitors” and issued on October 5, 2010 based on U.S. Application No. 11/080,992 (“the '992 Application”), which was filed on March 15, 2005. The '689 patent purports to claim priority to U.S. Provisional Patent Application No. 60/553,571 (“the '571 Application”), filed March 15, 2004 and to U.S. Provisional Patent Application No. 60/629,524 (“the '524 Application”), filed on November 18, 2004. The '689 patent lists Zhiyuan Zhang, Bruce J. Elder, Paul K. Isbester, Grant J. Palmer, and Luckner G. Ulysse as the inventors. I have been informed and understand that the '689 patent expires on June 27, 2028 according to the FDA publication, “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”).

41. I have been instructed and understand that in response to Torrent’s Interrogatory No. 1 to Takeda inquiring as to the date of conception and reduction to practice, Takeda did not

identify a reduction to practice date earlier than the filing dates of the '571 and '524 Applications, to which the '689 patent claims priority. (*See* Takeda's Objections and Responses to Defendants' First Set of Interrogatories (Nos. 1-10) dated November 20, 2017, at 4-5, Response to Interrogatory No. 1.) I understand from this that for purposes of this Report, I should consider the priority date of the '689 patent to be November 18, 2004 (which is the filing date of the '524 Application). However, even if the priority date is determined later to be March 15, 2004 (the filing date of the '571 Application) by a court, my conclusions on invalidity would be unaffected for all the reasons discussed in my Report.

B. Prosecution History of The '689 Patent

42. The '992 Application was originally filed with 161 claims. ('689 Patent File History, at Claims dated March 15, 2003). On June 19, 2007, the Examiner issued a restriction requiring an election by the Applicant as between two groups of claims. (Office Action dated June 19, 2007, at 2-6). In response to the restriction requirement, the Applicant amended claim 1 to specifically relate to compounds of the formula below. (*See* July 19, 2007 Amendment, at 2, 25). The Applicant cancelled claims 2-161 and added claims 162-276. (*Id.* at 3-24).



43. On August 8, 2007, the Applicant filed a Preliminary Amendment amending claims 165, 168, 169, 172, 179, 185, 193, 195, 201, 205, and 260 prior to the examination. (August 8, 2007 Preliminary Amendment at 3-23). On October 16, 2007, the Examiner

withdrew the restriction requirement, but rejected claims 1 and 162-276 under 35 U.S.C. § 112, ¶ 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention because the terms “esters,” “tautomers,” and “prodrugs” are not clear. (*See* Non-Final Rejection dated October 16, 2007, at 3-4). Claims 162, 163, 166, 167, 170 and 171 were rejected for not further limiting the claim from which they depend because claim 1 does not recite stereoisomers. (*Id.* at 4). In response, the Applicant amended claims 1 and 162-276 to delete reference to “esters,” “tautomers,” and “prodrugs.” (January 14, 2008 Amendment, at 1-21). Claims 1 and 165, 169, 173, 191, 197 and 214 were also amended to recite “including all stereoisomers … thereof.” (*Id.*). The Examiners also rejected claims 1 and 162-276 under 35 U.S.C. § 112, ¶ 1 for lack of enablement. (Non-Final Rejection dated October 16, 2007, at 7-8). In response, the Applicant amended claims 1, 164, 165, 168, 169, 172, 173, 179, 185, 191, 193, 195, 197, 201, 205 and 214 to delete the references to esters and polymorphs and references to prodrugs and solvates. (January 14, 2008 Amendment, at 1-21).

44. The Examiner did not find the Applicant’s argument persuasive and maintained rejection over claims 1, 162-208, 214-216, 218-225, 231-233, 235-242, 248-250 and 252-276 as being indefinite and rejection over claims 160-276 as being lack of enablement. (Final Rejection dated April 11, 2008 at 2-28). The Examiner also rejected claims 197-208 as being a substantial duplicate of claims 191-196. (*Id.* at 28-29). In response, the Applicant canceled claims 191-196, 209-213, 217-230, 234-247 and 251-259; and amended claims 1, 164, 165, 169, 173, 197, 214 and 215 to recite “or stereoisomers … thereof” and “or pharmaceutically acceptable salts thereof.” (July 11, 2008 Amendment, at 16-17). The Applicant also amended claims 260 and 273 to delete reference to polymers, solvates, esters, tautomers, enantiomers and prodrugs, and amended

claims 216, 233 and 250 to recite only “breast cancer.” (*Id.*).

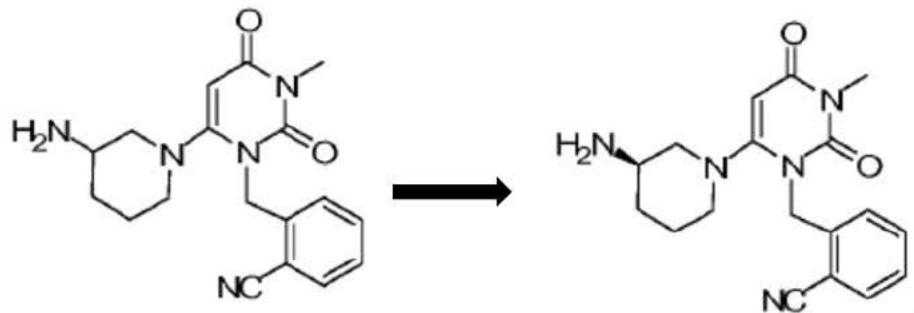
45. The Examiner withdrew the Finality of the Final Office Action, but still rejected all the pending claims. (August 19, 2008 Non-Final Rejection at 2-3). Specifically, the Examiner rejected claims 173-190 as being indefinite, claims 197-208 as being lack of enablement, and claims 1 and 162-190 are rejected as allegedly being anticipated by Schilling et al. (CA 143:347172, 2005) (*see also*, US 7,304,086 and US 7,371,871). (*Id.*). In response, the Applicant amended claims 173, 179 and 185 to recite that the pharmaceutical composition includes “one or more compounds selected from the group consisting of excipients, diluents, lubricants, binders, adjuvants, carriers, wetting agents, emulsifying agents, solubilizing agents and pH buffering agents.” (November 19, 2008 Amendment at 16.) The Applicant argued that the disclosure relied upon by the Examiner was derived directly from Applicant’s own work and dated after the earliest priority date of the pending application, and it only refers to the claimed compound alogliptin using their internal registration number “SYR-322.” (*Id.* at 17).

46. The Examiner maintained the rejection over claims 197-208 under 35 U.S.C. § 112, ¶ 1 for lack of enablement. (Non-Final Rejection dated January 9, 2009 at 2). The Examiner also rejected claims 1 and 162-190 under 35 U.S.C. §102(e) as being anticipated by Schilling et al., CA 143: 347172 (2005), US 7,304,086, and WO 2005/075436; and rejected claims 1, 162-190, 197-208, and 260-276 under 35 U.S.C. § 103(a) as being obvious over Schilling et al., CA 143:347172 and WO 2005/075436. (*Id.* at 19-20). In response to the lack of enablement rejection, the Applicant amended claims 199, 203 and 207 to recite that the article of manufacture may comprise a label indicating “a disease state for which the compound is to be administered wherein the disease state is diabetes.” (April 9, 2009 Amendment at 16). In response to the anticipation rejection, the Applicant argued that the teaching of SYR-322 did not

appear in the priority document relating to WO 2005/075436 until February 4, 2005, which is later than the priority date for SYR-322 (March 15, 2004). (*Id.* at 16-17).

47. The Examiner found the Applicant's argument unpersuasive and maintained the rejection under 35 U.S.C. §§102(e) and 103(a). (*See* Non-Final Rejection dated August 7, 2009 at 2-5). The Examiner also rejected claims 1, 162-190, 197-208, 214-216, 231-233, 248-250 and 260-276 on the ground of (nonstatutory) obviousness-type double patenting as being unpatentable over claims 1-6, 25-32, 34-39, 43, 49-54, 72-76, 78-83 and 87 of co-pending Application No. 11/928,944. (*Id.* at 6). In response, Applicant cancelled claims 251-276. (November 9, 2009 Amendment at 11.) With respect to the rejection under 35 U.S.C. §§ 102(e) and 103(a), Applicant argued that "Schilling's disclosure of 'SYR-322' is after Applicant's priority date for the pending claims" and neither Schilling nor CA 143: 347172 is prior art. (*Id.* at 14-15).

48. On February 24, 2010, a notice of allowance was issued to the then pending claims 1, 162-190, 197-208, 214-216, 231-233, and 248-250. On February 22, 2012, Applicant submitted a Request for Certificate of Correction to correct the structure recited in claims 4, 12, 19, 25, 35 and 39 to show the stereochemistry for the 3-aminopiperidiny1 group:

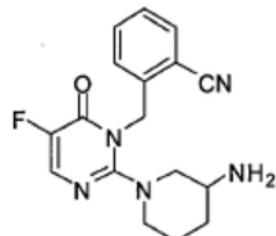


VI. The Obviousness-Type Double Patenting Reference: The Feng Patent

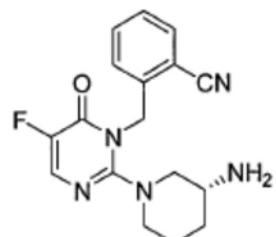
49. The Feng patent is entitled “Dipeptidyl Peptidase Inhibitors” and issued on May 25, 2010 based on U.S. Application No. 10/918,327 (“the ’327 Application”), which was filed on August 12, 2004. The Feng patent claims priority to U.S. Provisional Patent Application No. 60/495,238, filed on August 13, 2003. I understand that the Feng patent is prior art over the ’689 patent under what is pre-AIA 35 U.S.C. § 102(e). The Feng patent shares a common inventor (i.e., Zhiyuan Zhang) with the ’689 patent.

50. The ’327 Application was filed with 230 original claims. On April 9, 2007, the Applicant added 4 new claims (claims 231-234). In response to a non-final rejection, on October 13, 2008, the Applicant cancelled certain claims, and added new claims 235-242 “to more completely cover certain aspects of the present invention.” (October 13, 2008 Amendment, at 39). Among these newly-added claims, claims 235 and 236 recite a compound with a specified formula reproduced below:

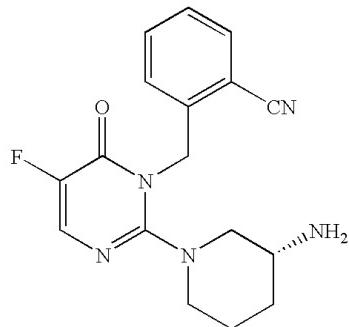
235 (New). A compound having the formula:



236 (New). A compound according to claim 235 having the formula:



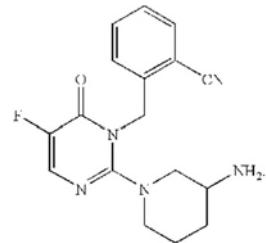
51. The Applicant also noted that “[s]upport for the new claims can be found, for example, in Example 30 of the specification.” (*Id.*). Example 30 of the specification refers to 2-[2-(3-(R)-Amino-piperidin-1-yl)-5-fluoro-6-oxo-6H-pyrimidin-1-ylmethyl]-benzonitrile, which has the same formula as recited in claim 236:



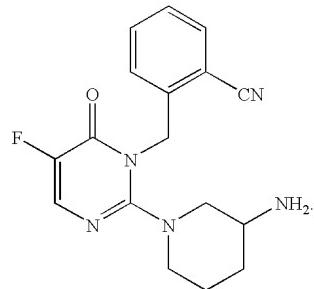
52. After the final rejection, the Applicant filed a request for continued examination (RCE) on May 27, 2009, which included claims 235-236 as “previously presented” claims. (May 27, 2009 Amendment, at 33). On June 11, 2009, the examiner rejected certain pending claims under non-statutory obviousness-type double patenting as being unpatentable over select claims of the then co-pending Patent Application No. 10/918,317. On October 12, 2009, the Applicant filed a terminal disclaimer over the Patent Application No. 10/918,317 and cancelled some claims. On January 4, 2010, the Examiner issued a Notice of Allowance and allowed all the then-pending claims, including claims 235-236 as reproduced as above. (Notice of Allowance dated January 4, 2010 at 4).

53. On May 5, 2010, claims 235-236 issued as claims 161-162 of the Feng Patent. However, due to an obvious ministerial error, the formula recites in claim 162 does not show the stereochemistry for the 3-aminopiperidinyl substituent, which results a formula identical to claim 161. Claims 161 and 162 are reproduced as follows:

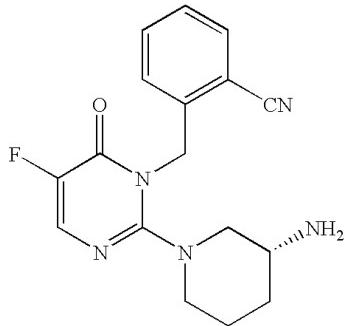
161. A compound having the formula:



162. A compound according to claim 161 having the formula:



54. Thus, it would be immediately apparent to a POSA that a clerical error was made in the formula drawing of claim 162, since it should reflect the same identical stereochemistry in the 3-aminopiperidinyl substituent as in then-pending claim 236 (that issued as claim 162). In addition, claim 162 does not make sense if it is identical to and a duplicate of claim 161 and therefore both of the issued claims (161 and 162) have the same scope even though claim 162 directly depends from claim 161. Moreover, in all the Examples of the specification that contain the 3-aminopiperidinyl group, including Example 30 which is the support for claims 162, the 3-aminopiperidinyl group is shown as its “R” enantiomer. (Feng patent at 66:44-99:66). Therefore, for purposes of this Report, I consider claim 162 (as it would also readily be understood by a POSA) to recite “[a] compound having the formula” as follows:



VII. CLAIM CONSTRUCTION

55. I have been advised that the '689 patent claims are to be given their ordinary and customary meaning as they would have been understood by the POSA. I have followed these principles in my analysis described throughout this Report. Although the '689 patent provides definitions for certain claim terms, those definitions are conventional.

56. For purposes of this Report, no construction is necessary for claim 162 of the Feng patent. I simply note that, as explained in paragraphs 53-54 above, claim 162 of the Feng patent actually claims (and should be construed to claim) a compound with the proper stereochemistry for the 3-aminopiperidinyl substituent as illustrated above.

VIII. BASES FOR MY OPINION OF OBVIOUSNESS-TYPE DOUBLE PATENTING

A. Understanding of the Applicable Legal Principles

57. I have been instructed and understand that obviousness-type double patenting is a legal doctrine adopted to prevent the issuance of patent claims that are not patentably distinct from one or more claims in a second and earlier expiring patent. A later claim is not patentably distinct from an earlier claim if it is obvious over the earlier claim. If any differences exist between the later claim and the earlier claim, the later claim is invalid if those differences would have been obvious. For example, patentable differences do not exist when later claims represent minor linguistic differences, obvious variations, or are merely a subset of the earlier claims. The

purpose of the doctrine is to prevent a party from obtaining a patent for an obvious modification of an earlier invention and therefore, improperly extending the patent term of the earlier invention. I have been informed and understand that a later compound claim may be invalid for obviousness-type double patenting over an earlier compound claim.

58. I have been informed and understand that the obviousness-type double patenting analysis involves two steps. First, the court construes the claim in the earlier patent and the claim in the later patent and construes the differences. Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct. Two claims are not “patentably distinct” if the later claim would have been obvious to a person of ordinary skill in the art based on the earlier claim, in light of additional prior art.

59. I have been informed and understand that the obviousness-type double patenting analysis is similar to an obviousness analysis under 35 U.S.C. § 103, but that there are some differences. First, an obviousness inquiry compares the claimed subject matter to the prior art, whereas an obviousness-type double patenting inquiry compares the claims in dispute to the subject matter claimed in an earlier patent. I also understand that in the context of the obviousness-type double patenting, the POSA is considered to have knowledge of and be in possession of the inventions claimed in the earlier patent and may rely on the knowledge in the art at the time of the alleged invention. I understand that, generally, only the claims of the earlier patent are considered in the context of the obviousness-type double patenting. While the disclosure in the specification of the earlier patent may not be used as prior art in a double-patenting analysis, the disclosure may be used to construe and thus determine the scope of the claims at issue in the earlier patent, and to answer the question whether claims in the later patent merely define an obvious variation or variant of what is previously claimed.

60. Additionally, I understand that when analyzing obviousness-type double patenting in cases involving claimed chemical compounds, the issue is not whether a POSA would have selected the earlier claimed compound as a lead compound; the analysis must focus on the earlier claimed compound over which double patenting has been alleged, whether it is a lead compound or not. I have been informed and understand that in cases involving claimed chemical compounds, an analysis of non-statutory obviousness-type double patenting asks whether a POSA would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success. I have also been informed and understand that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art as long as there was a reasonable probability of success; a guarantee of success is not required.

61. I have also been informed and understand that evidence of secondary considerations may be considered when offered in an obviousness-type double patenting analysis. Secondary considerations of nonobviousness include commercial success, long-felt but unsolved needs, failure of others, copying, unexpected results, industry acclaim, and skepticism of others. To overcome a prima facie case of obviousness, the patentee must establish a nexus between any alleged evidence of secondary considerations of nonobviousness and the claims of the patent. There is no nexus unless the offered secondary consideration actually results from something that is both claimed and novel in the claim. I have also been informed and understand that, to overcome a prima facie case of obviousness, any alleged secondary considerations must also be commensurate in scope with the claimed invention.

B. Person of Ordinary Skill in the Art

62. I understand that in order to assess whether there would have been a reason or

motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success in the obviousness-type double patenting analysis, I must step backward in time and into the shoes worn by the hypothetical POSA when the alleged invention was at yet unknown (just before it was made), which I understand would be before November 18, 2004 for this matter. I understand as discussed above that there is another date also of March 15, 2004, but whether I step backwards in time and into the shoes of a POSA just prior to March 15, 2004 or just prior to November 18, 2004, my conclusions on invalidity would be unaffected.

63. I am informed that this POSA is a hypothetical person that is constructed in a manner where the POSA is presumed to be aware of the state of the art and all of the relevant prior art and who thinks along the conventional wisdom of those in the art. I am informed that the latter means that the POSA is not a simple automaton but a person of ordinary creativity. This means the POSA is not simply a pair of hands following directives but presumed to have an understanding of the prior art and its technical implications, as well as the problems faced by those working in the field, and is able to apply common knowledge to attempt to solve a given problem.

64. I have been informed and understand that factors that may be considered in determining the level of ordinary skill in the art may include: (A) type of problems encountered in the art; (B) prior art solutions to those problems; (C) rapidity with which innovations are made; (D) sophistication of the technology; and (E) educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate.

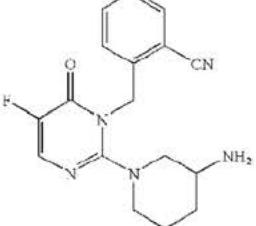
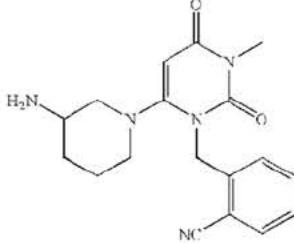
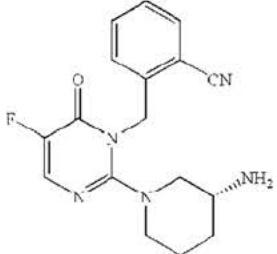
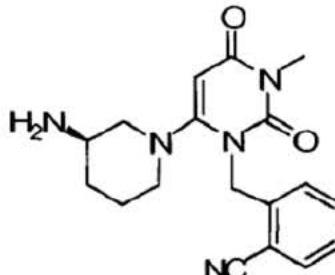
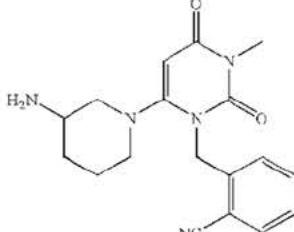
65. Based on my knowledge and experience, it is my opinion in reviewing the '689

patent claims and specification that the POSA with respect to the subject matter of the '689 patent is a person with a Ph.D. or an equivalent advanced degree in medicinal and/or organic chemistry (or a closely related discipline such as pharmaceutical chemistry), having at least several years of relevant practical academic or industrial experience researching and developing drugs for treating type 2 diabetes. The POSA could have had a lower level of formal education if such a person had a higher degree of relevant academic or industrial experience. This experience and knowledge may come from the POSA's own knowledge and experience, or through access to or guidance from individuals with either doctoral or medical degrees in pharmacy/pharmacology or medicine respectively. I understand that this POSA is presumed to be aware of all the pertinent art at the time of the invention was made. The POSA in my opinion should have no trouble understanding the relevant references in the art and would be able to draw appropriate inferences from them and from those others of skill in the art including those he or she may ordinarily collaborate with on matters.

C. Claims 1, 3, 4, 9, 11-12, 43 and 49 of the '689 Patent Are Not Patentably Distinct from Claim 162 of the Feng Patent in View of Kim 1998

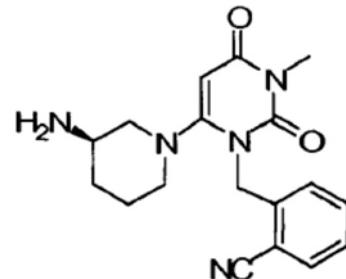
66. It is my opinion that claims 1, 3, 4, 9, 11-12, 43 and 49 of the '689 patent are not patentably distinct from claim 162 of the Feng patent in view of Kim 1998 and in view of the knowledge in the art and are thus invalid under obviousness-type double patenting. In particular, it is my opinion that it would have been obvious to a POSA to modify the claimed compound in claim 162 of the Feng patent to arrive with a reasonable expectation of success (without the benefit any hindsight) at the compound known as alogliptin that is claimed in the asserted claims of the '689 patent.

67. Claims 161 and 162 of the Feng patent and the asserted claims of the '689 patent are reproduced in the following table:

Claims 161 and 162 of the Feng Patent	Asserted claims of the '689 patent
<p>161. A compound having the formula:</p> 	<p>1. A compound of the formula</p>  <p>or stereoisomers or pharmaceutically acceptable salts thereof.</p> <p>3. The compound according to claim 1, wherein the compound comprises a single stereoisomer.</p>
<p>162. A compound according to claim 161 having the formula:</p> 	<p>4. A compound of the formula</p>  <p>or pharmaceutically acceptable salts thereof.</p> <p>9. A compound of the formula</p>  <p>wherein the compound is present as a benzoate salt, or stereoisomers thereof.</p> <p>11. The compound according to claim 10, wherein the compound is</p>

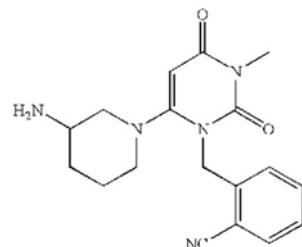
present as a single stereoisomer.⁵

12. A compound of the formula



wherein the compound is present as a benzoate salt.

43. A method of treating type II diabetes in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of the formula

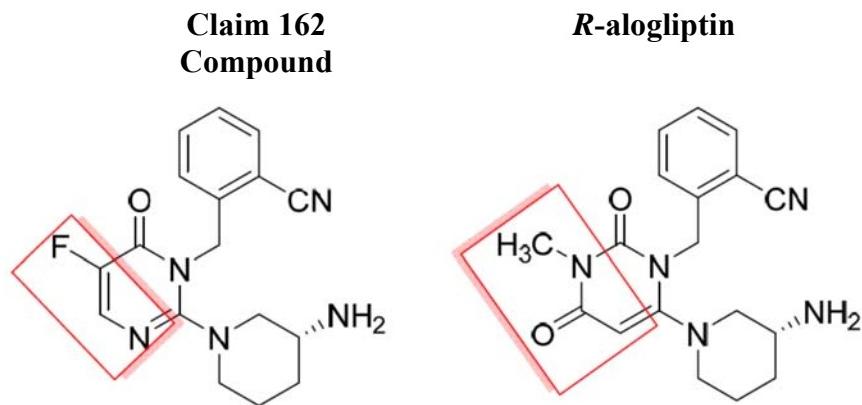


or stereoisomers or pharmaceutically acceptable salts thereof.

49. A method of treating type II diabetes in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound according to claim 12.

⁵ Claim 11 depends on claim 10, which recites “[t]he compound according to claim 9, wherein the compound is present as a mixture of stereoisomers.”

68. As shown in the table above, independent claims 4 and 12 of the '689 patent are directed to *R*-alogliptin and/or its pharmaceutically acceptable salts (claim 4) or benzoate salt (claim 12), whereas independent claims 1 and 9 of the '689 patent are directed to the two enantiomers of alogliptin compounds and their pharmaceutically acceptable salts or benzoate salt. Claim 43 is directed to a method of treating Type II diabetes using the compounds recited in claim 1. A side-by-side comparison of the formula of the pyrimidinone-based compound recited in claim 162 (hereafter, "the pyrimidinone-based compound") and *R*-alogliptin (i.e., the compound recited in claims 4 and 12 of the '689 patent) is shown below:



69. As also shown in the figure above, the only difference between the structures of the pyrimidinone-based compound and *R*-alogliptin is in the center of the two compounds in the area highlighted by the red box. Alogliptin has a uracil-ring with a methyl group at the N3 position, whereas the pyrimidinone-based compound has a pyrimidinone-ring with a fluorine at the C3 position. Therefore, the double-patenting analysis comes down to the question of whether a POSA based on the Claim 162 Compound (but not *R*-alogliptin) would have found it obvious to make a modification that entails replacing in the claim 162 compound the "pyrimidinone-structure core with a fluorine at the N3 position" with a "uracil-structure core with a methyl group" in light of the teaching in the art.

70. In my opinion, such replacement would have been to a POSA a logical, routine and obvious modification based on the teachings in Kim 1998 and the common knowledge in the art.

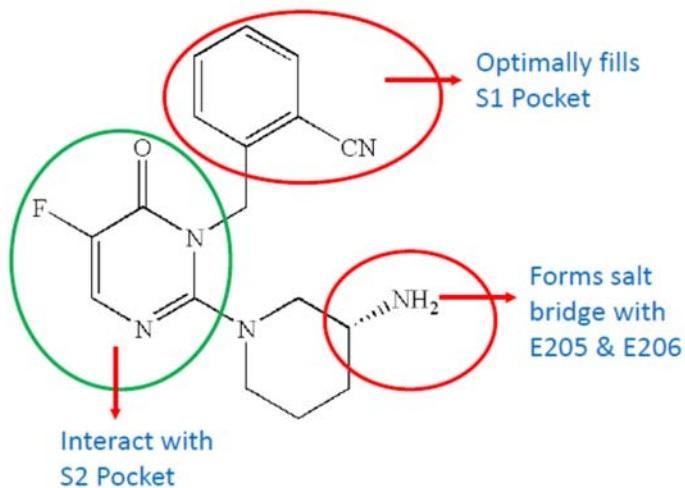
71. As an initial matter, based on the structure information of DPP-IV and its known inhibitors, the POSA seeking to develop a highly specific and potent DPP-IV inhibitor drug for the treatment of type 2 diabetes, starting with the pyrimidinone-based compound (claim 162), would have been motivated to optimize only the pyrimidinone core of the compound and maintain the rest of the compound. The reasons are explained further below.

72. The POSA would have retained the 2-cyanobenzyl group on the pyrimidinone-based compound based at least on the observation by Kanstrup 2003 that this substituent structure element suitably occupies the S1 binding pocket of DPP-IV and was used in a number of examples claimed in Kanstrup 2003. (*See supra ¶31*). The POSA would also have kept the 3-aminopiperidinyl group untouched because the prior art teaches that in non-peptide DPP-IV inhibitors the amine group on the 3-aminopiperidinyl group is key for inhibitor binding because it forms an ionic bond via a salt bridge with the two glutamic acid residues, E205 and E206, on DPP-IV by orienting the amino group to interact with these residues. (Wiedeman at 418; Aertgeerts at 415). Moreover, in the prior art it is taught that many xanthine-based compounds with both 2-cyanobenzyl and aminopiperidinyl groups have shown good DPP-IV inhibition activity. (CA '730 at 99, 197; Mark 2004 at pp. 135-185; Kanstrup 2003 at 23-24).

73. For at least the reasons above, the POSA would have been motivated to maintain both 2-cyanobenzyl and aminopiperidinyl groups on the pyrimidinone-based compound. Accordingly, the POSA would have been motivated to only alter the core that contained the pyrimidinone ring. In other words, the POSA would have been motivated to and would have

sought to alter the pyrimidinone-based compound through a scaffold replacement to alter only the core structure in an attempt to create a novel, potent DPP-IV inhibitor.

74. From structure-based information of DPP-IV and its inhibitors, which show the inhibitor recognition and interactions with DPP-IV, the POSA would have understood that the core of the pyrimidinone-based compound (the structure on the compound that the POSA would have wanted to alter) must be responsible for interacting with key amino acids in the S2 pocket of DPP-IV. The structure of the pyrimidinone-based compound and the interactions of each of its parts with DPP-IV are illustrated in the diagram below.



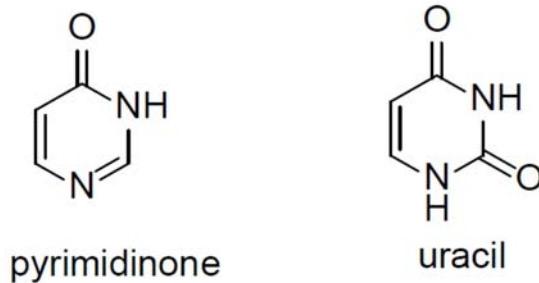
75. The prior art teaches that the hydrophobic S2 pocket of DPP-IV is determined by the side chains of Arg 125, Phe 357, Tyr 547, Pro 550, Tyr 631, and Tyr 666. (*supra* ¶ 26). Notably, four of the six residues are amino acids with a hydrophobic aromatic ring. Accordingly, it would have been obvious for the POSA to look for a core structure that would be able to optimally fill into the hydrophobic core of the S2 pocket of DPP-IV, which consists of many aromatic amino acids.

76. The prior art teaches that uracil has potent anti-diabetic activity. Kim 1998

expressly teaches that the anti-diabetic effect of uracil is similar to commercially available anti-diabetic drug Daonil®. While Kim 1998 reported three anti-diabetic agents—uracil, rutin and ascorbic acid—a POSA seeking to develop a new DPP-IV inhibitor class drug for the treatment of type 2 diabetes would have considered only uracil for use as a potential DPP-IV-inhibitor. This is because a POSA would have readily understood that the structures of the other two compounds (rutin and ascorbic acid) would make them unlikely to bind to DPP-IV. This is because these two compounds are both very polar and therefore would be unlikely to occupy important hydrophobic binding sites on DPP-IV.

77. Kim 1998 does not directly teach that uracil's anti-diabetic effect was based on DPP-IV inhibition activity. The POSA would have nonetheless identified uracil as a good candidate scaffold for incorporating into a DPP-IV inhibitor and reasonably expect that it would result in a potent DPP-IV inhibitor. This is because a POSA, who is seeking to develop a new DPP-IV inhibitor class drug via scaffold replacement and fragment-based screening approaches, would have readily recognized the uracil ring as a part of the purine scaffold of the DPP-IV inhibitors disclosed in Wiedeman, Kanstrup 2003 and Mark 2004. (*See supra ¶¶ 29-34*).

78. As discussed in paragraphs 74-75 above, the hydrophobic S2 pocket of DPP-IV, which consists of many aromatic amino acids, is key for inhibitor recognition and binding. Accordingly, the POSA would have readily recognized that a uracil scaffold would be able to suitably fill into the hydrophobic S2 pocket and thus be a good candidate scaffold for incorporating into a DPP-IV inhibitor because it has a similar size and shape compared to a pyrimidinone ring.

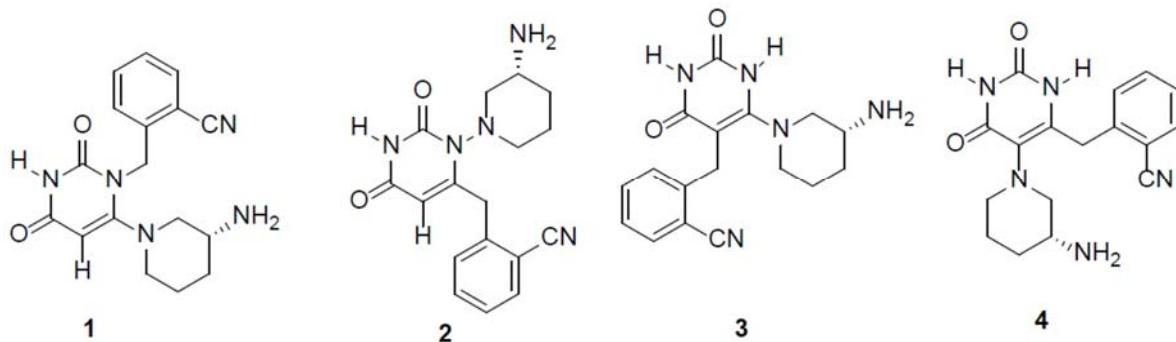


79. Accordingly, the POSA would have been motivated to replace the pyrimidinone scaffold in the compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil) (see figure above for both structures). This scaffold replacement approach would have been reasonably expected by the POSA to optimize the DPP-IV inhibitor due to uracil's known anti-diabetic effect and potential to bind to the active site of DPP-IV by forming similar binding interactions with aromatic amino acids in the S2 pocket of DPP-IV.

80. The POSA would have also separately (but additionally) been motivated to directly replace the pyrimidinone scaffold in the compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil). This is because at the time of invention, it was commonly known in the art that a fluoroolefin mimics an amide bond in DPP-IV inhibitors, *i.e.*, a replacement of fluoroolefin moiety with amide bond would result in an active DPP-IV inhibitor. (See Evans at 578 (noting that “[i]t is reported that the fluoroolefin mimics an amide bond” in DPP-IV inhibitors)). As illustrated above in the figure in paragraph 69, the pyrimidinone-based compound in claim 162 of the Feng patent has a fluoroolefin moiety in the pyrimidinone-ring. Thus, the POSA seeking to develop a new DPP-IV inhibitor class drug for the treatment of type 2 diabetes, starting with the pyrimidinone-based compound in claim 162, would have naturally been motivated to replace the fluoroolefin moiety in the pyrimidinone-ring with the amide bond, which results in a uracil ring in the core structure. The POSA would have had reasonable

expectation that this modification would yield a compound with potent DPP-IV inhibiting activity.

81. In the former scenario (*supra ¶¶ 76-79*), by using the pyrimidinone-based compound as recited in claim 162 of the Feng patent as a starting point, the POSA could in theory replace the pyrimidinone ring (*i.e.*, only the nitrogen, carbon and oxygen atoms)⁶ with the uracil ring system in four different ways to arrive at the structures below:



82. However, the POSA would readily understand that not all of the four compounds are practicable viable options for purposes of arriving at a DPP-IV inhibitor for use in a drug for treatment of type II diabetes. As an initial matter, the POSA would have recognized that Uracil analogue (2) particularly undesirable since it was well-known that hydrazine derivatives tend to be mutagenic and carcinogenic. *See, e.g.*, S. Parodi, *et al.*, “DNA-damaging Activity In Vivo and Bacterial Mutagenicity of Sixteen Hydrazine Derivatives as Related Quantitatively to their

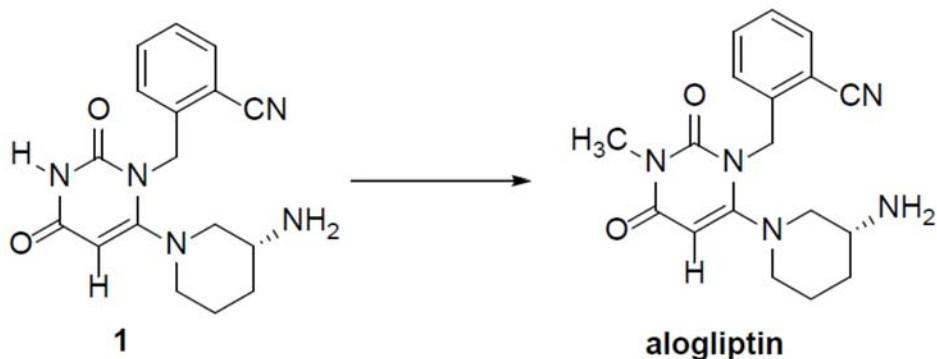
⁶ The POSA seeking to replace the scaffold would have only focused on the nitrogen, carbon and oxygen atoms, and would have not kept the fluorine atom attached to the scaffold, because the POSA would have recognized that fluorine is extremely electronegative and *N*-fluoro is highly electrophilic, reactive and thus not stable. (*See* Lal et al., “Electrophilic NF Fluorinating Agents,” Chemical Reviews, 1996, Vol. 96, No. 5, pp. 1737-1755. (“Lal 1996”) at 1753.) The POSA would have therefore considered the *N*-fluoro undesirable because fluorine can react with nucleophiles, such as amino- or hydroxyl groups found in amino acids and other biological molecules. (*Id.* at 1738).

Carcinogenicity,” Cancer Research 41, 1469–1482, April 1981 (“Parodi 1981”).

83. Further, as discussed above (*supra ¶¶ 72-73*), the POSA would have been motivated to keep both 2-cyanobenzyl and the 3-aminopiperidinyl group with their relative spatial relationship unchanged to keep its DPP-IV inhibiting activity. Because the structure and adjacent arrangement of 2-cyanobenzyl, 3-aminopiperidinyl group, and the carbonyl group of Uracil analogue (1) has a closer analogy to the original pyrimidinone-based compound recited in claim 162 of the Feng patent, the POSA would have prioritized Uracil analogue (1) as an option for further modification, while further optimizing Uracil analogues (3) and (4).

84. Alternatively, in the latter scenario (*supra ¶ 80*) where the POSA was separately motivated to replace the fluorolefin moiety in the pyrimidinone-ring with the amide bond, the POSA would have readily only arrived at Uracil analogue (1) directly.

85. The POSA who was seeking to optimize the core structure of the pyrimidinone-based compound to improve its potency and selectivity as a DPP-IV inhibitor would have also been motivated to replace the N3-hydrogen substituent in the three Uracil analogues with a small hydrophobic group such as methyl (the smallest alkyl group) to better occupy the hydrophobic S2 site of DPP-IV. This substitution is a routine experimentation and would result in a finite number of identifiable N-alkyl analogues of Uracil analogues (1), (3) and (4), such as the N-methyl analogues. As explained above, a POSA would have prioritized Uracil analogue (1) for further optimization, and thus would have readily arrived at the N-methyl analogue of Uracil analogue (1), which is Alogliptin, as shown below:



86. In sum, it would have been to a POSA a logical, routine and obvious modification to modify the compound recited in claim 162 of the Feng patent (in view of Kim 1998 and the common knowledge known in the art) to arrive with a reasonable expectation of success at the compound that is claimed in the '689 patent—Alogliptin. In sum, it would have been obvious for the POSA to 1) replace the pyrimidinone ring in the compound recited in claim 162 of the Feng patent with a Uracil as suggested by Kim 1998 and/or the structure information of DPP-IV and its inhibitors commonly known in the art; and 2) replace the N3-hydrogen with a methyl group to enhance the hydrophobicity at the core center and better occupy the hydrophobic S2 site of DPP-IV. The POSA would have been motivated to make these modifications with a reasonable expectation of success that he or she would thereby obtain a selective DPP-IV inhibitor with increased potency.

87. It was well known in the art of pharmaceutical science that the formation of salts is invaluable for the preparation of safe and effective dosage form of many drugs. For example, it was well known in the art that the solubility and oral bioavailability of poorly water soluble basic drugs is generally improved by salt formation using inorganic or organic acids (such as hydrochloric acid or benzoic acid, respectively). (*See Berge et al., "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, Vol. 66, pp. 1-19 (1977)* ("Berge 1977"), at 7). Thus, it

would have been obvious for the POSA to prepare alogliptin in the form of pharmaceutically acceptable salt.

88. Claims 9, and 11-12 of the '689 patent recite benzoate salt forms of alogliptin, which does not add additional patentability to the claims. The benzoate salt form is a salt form that has been commonly used in the pharmaceutical field. In fact, the '689 patent specification states that “[a]ctual methods of preparing such dosage forms are known in the art, or will be apparent, to those skilled in this art; for example, *see* Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975.” '689 patent at col. 51, ll. 62-66. Furthermore, “benzoic acid” was also listed as one of the organic acids to prepare pharmaceutically acceptable salts for the compounds claimed in the Feng patent. (*See* Feng patent at 11:26-36). It was further well-known at the time when the invention was made that there were only 53 FDA approved acid addition salt forms—one of which was the benzoate salt form. *See Id.*, Table I. In addition, Kanstrup 2003 also discloses that benzoate may be used as the salt form for the DPP-IV inhibitors disclosed therein. *See* Kanstrup 2003 at p. 18, ll. 25-33.

89. Accordingly, it is my opinion that claims 1, 3, 4, 9 and 11-12 of the '689 Patent are not patentably distinct from claim 162 of the Feng patent in view of Kim 1998 and in view of the common knowledge in the art.

90. Claims 43 and 49 of the '689 Patent are directed to a method of treating type II diabetes in a patient in need thereof with the compounds claimed in claims 1 and 12. As explained earlier, it was common knowledge that DPP-IV inhibitors have been used in treatment of type 2 diabetes. It would have been obvious for a POSA to administer alogliptin (or alogliptin benzoate) in the form of a pharmaceutical composition to a patient in need of treatment of type II diabetes. Accordingly, claims 43 and 49 of the '689 Patent are also not patentably distinct from

claim 162 of the Feng patent in view of Kim 1998 and in view of the common knowledge in the art.

IX. SECONDARY CONSIDERATIONS

91. It is my opinion that there are no secondary considerations that overcome my opinions that claims 1, 3, 4, 9, 11-12, 43 and 49 of the '689 Patent are invalid for obviousness-type double patenting over claim 162 of the Feng patent in View of Kim 1998 and common knowledge in the art. I have been informed that it is Plaintiffs' burden to present any evidence of secondary considerations to rebut the obviousness-type double patenting. I have also been informed that Plaintiffs have not asserted commercial success as evidence of secondary considerations. To the extent that Plaintiffs seek to rely on any evidence of secondary considerations in their expert reports, I reserve the right to address them in a later report in accordance with the schedule in this case.

X. SUPPLEMENTATION AND REBUTTAL

92. This Report sets forth my professional opinions based only on information available as of the date that I have signed this Report below. In the event that additional data or testimony is made available, I may find it appropriate to revise or supplement my opinions. I also reserve the right to clarify, amend or supplement my opinions in response to any issues raised by Plaintiffs, evidence presented by them, or any additional information that I become aware of later or may be made available to me in the future, including documents or information produced in this litigation, or information disclosed at depositions or set forth in any reports submitted by Plaintiffs' experts.

93. I expect to be called to testify at trial in the above-captioned consolidated actions regarding the matters set forth in this Report. If called to testify at trial, I may explain principles

and terminology referred to or related to issues in this Report, as well as any of the documents referenced in the Report. I reserve the right to convey my opinions through the use of demonstrative exhibits at trial. I have not yet created all of the exhibits I may use at trial, but if I choose to, such exhibits may be of varying scope in order to assist in explaining what is set forth in my reports and as needed to respond to any opinions raised by Plaintiffs' experts in their reports or during their depositions. I may also comment on or testify at trial in response to the testimony of other witnesses, including witnesses who testify on behalf of Plaintiffs at trial or during depositions.

94. I reserve the right to testify, expound on and/or express further opinions on issues or matters related to my opinions in this Report or later raised in this litigation, including as necessary (1) to rebut any matters testified to by Plaintiffs' experts or opinions including as expressed by Plaintiffs' experts in their expert reports; (2) during my deposition; and (3) at trial.

XI. CONCLUSION

95. As set forth above in this Report, and as also confirmed based on my own knowledge and experience, it is my opinion that from the perspective of a POSA, claims 1, 3, 4, 9, 11-12, 43, and 49 of the '689 patent are not patentably distinct from claim 162 of the Feng patent in view of Kim 1998 and the common knowledge in the art, and therefore, are invalid for obviousness-type double patenting.

Signed this 7 day of June, 2019.



DAVID P. ROTELLA, PH.D.

EXHIBIT A**Materials Considered**

Description	Document Production Range
U.S. Patent No. 7,807,689	TAK-ALOG 00413714 - TAK-ALOG 00413768
Portions of File History of U.S. Patent No. 7,807,689	TAK-ALOG_00156012 - TAK-ALOG_00186127
U.S. Patent No. 7,723,344 to Feng et al. "Dipeptidyl Peptidase Inhibitors" issued on May 25, 2010	TOR-NESINA 00127019-TOR-NESINA 00127088
Portions File History of U.S. Patent No. 7,723,344	TOR-NESINA 00142001-TOR-NESINA 00143216
Kanstrup <i>et al.</i> , WO 03/004496 entitled "DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes", published January 16, 2003	IndAlo0000738-IndAlo0000839
Evans, Michael D., "Dipeptidyl peptidase IV inhibitors" IDrugs 2002 5(6):577-585	IndAlo0000840-IndAlo0000848
Anderson, Amy C. "The Process of Structure-Based Drug Design" Chemistry & Biology, Vol. 10, 787-797, (September 2003)	IndAlo0000966-IndAlo0000976
McGaughey, Georgia B., et al., "π-Stacking Interactions," The Journal of Biological Chemistry, Vol. 273, No. 25, Issue of June 19, pp. 15458–15463 (1998)	TOR-NESINA 00126996-TOR-NESINA 00127002
Bohm et al., "Scaffold hopping," Drug Discovery Today: Technologies 2004, Vol. 1, No. 3, 217-223 (December 2004)	TOR-NESINA 00127789-TOR-NESINA 00127796
Aertgeerts, K., et al., "Crystal structure of human dipeptidyl peptidase IV in complex with a decapeptide reveals details on substrate specificity and tetrahedral intermediate formulation", 13(2) PROTEIN SCI. 412-421 (Feb. 2004)	TOR-NESINA 00126326-TOR-NESINA 00126335
Engel, M., et al., "The crystal structure of dipeptidyl peptidase IV (CD26) reveals its functional regulation and enzymatic mechanism", 100(9) PNAS 5063-5068 (Apr. 29, 2003)	IndAlo0000946-IndAlo0000951
Lambeir, A., "Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV", 40(3) Crit. Rev. Clin. Lab. Sci. 209-294 (2003)	IndAlo0000858-IndAlo0000945
Wiedeman, P.E. & Trevillyan, J.M., "Dipeptidyl peptidase IV inhibitors for the treatment of impaired glucose tolerance and type 2 diabetes", 4(4) Current Opinion in Investigational Drugs 412-420 (Apr. 2003)	IndAlo0000849-IndAlo0000857

C.A. Patent No. 2,496,249 to Mark et al., entitled “8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments,” published on March 4, 2004 (“Mark 2004”)	TOR-NESINA 00127532-TOR-NESINA 00127751
C.A. Patent No. 2,435,730 to Lotz et al., entitled “xanthines derivatives, the production thereof and their use as pharmaceutical compositions,” published on September 6, 2002 (“CA ’730”)	IndAlo0000374-IndAlo0000737
Kim et al., “Anti-diabetic Activity of Constituents of Lycii Fructus,” The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) (“Kim 1998”)	TOR-NESINA 00126805-TOR-NESINA 00126810
S. Parodi, <i>et al.</i> , “DNA-damaging Activity In Vivo and Bacterial Mutagenicity of Sixteen Hydrazine Derivatives as Related Quantitatively to their Carcinogenicity,” Cancer Research 41, 1469–1482, April 1981	TOR-NESINA 00126607-TOR-NESINA 00126621
Lal et al., “Electrophilic NF Fluorinating Agents,” Chemical Reviews, 1996, Vol. 96, No. 5, pp. 1737-1755	TOR-NESINA 00126976-TOR-NESINA 00126995
Berge et al., “Pharmaceutical Salts,” Journal of Pharmaceutical Sciences, Vol. 66, pp. 1-19 (1977)	TOR-NESINA 00127344-TOR-NESINA 00127364

EXHIBIT B

DAVID P. ROTELLA, Ph.D.

Margaret & Herman Sokol Professor of Medicinal Chemistry

Department of Chemistry & Biochemistry

Montclair State University

1 Normal Avenue

Montclair NJ 07043

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Summary of Accomplishments:

- **Montclair State University**-Obtained >\$2.5MM in research funding in three years
- **Wyeth Research**-led chemistry teams in CNS drug discovery projects and key leader for collaboration with Solvay Pharmaceuticals. Delivered a clinical candidate, managed chemists in group that delivered another.
- **Lexicon Pharmaceuticals**- Beginning from a screening hit, in less than one year, led project team that identified potent, selective, orally bioavailable inhibitors of PDE7A.
- **Bristol-Myers Squibb**-First to publish the discovery of novel phosphodiesterase type 5 inhibitors with better *in vitro* potency and selectivity compared to sildenafil. Contributed to discovery of 2 clinical candidates (PDE5 inhibitor, DPP4 inhibitor).
- **Cephalon**-Responsible for initial conception and development of several programs. Key leader in collaborations with Kyowa Hakko and Schering Plough. Discovered CEP 1347, which advanced to phase III trials for Parkinson's Disease.

Experience:

- **Montclair State University July 2011-present**
Margaret and Herman Sokol Professor of Chemistry, Department of Chemistry and Biochemistry; joint appointment in Sokol Institute of Pharmaceutical Life Sciences
- **Independent Consultant, February 2010-present**
Established consulting agreements with pharmaceutical companies and law firms to advance drug discovery programs and provide expert information on selected topics in drug development
- **Wyeth Research/Pfizer, 2005-February 2010**
Principal Research Scientist III, chemistry team leader. Directed up to 20 chemists. Member of Princeton Chemical Science leadership team.
- **Lexicon Pharmaceuticals, 2003-2005**
Senior Group Leader, responsible for multiple drug discovery programs. Directed up to 18 FTEs with 4 direct reports. Member of department leadership team.
- **Bristol-Myers Squibb PRI, 1997-2003**
Principal Scientist, cardiovascular and metabolic disease drug discovery
- **Cephalon, Incorporated, 1991-1997**
Group Leader, CNS and cancer drug discovery.
- **School of Pharmacy, University of Mississippi**
Assistant Professor, Department of Pharmacognosy 1987-1991
Adjunct Professor, Department of Medicinal Chemistry, 2009-present

- **School of Pharmacy, University of Pittsburgh**, 2010-present
Adjunct Professor, Department of Pharmaceutical Sciences
- **Center for Drug Discovery, Northeastern University**, 2010-present
Adjunct Professor

Education:

- Postdoctoral Scholar, Department of Chemistry, The Pennsylvania State University, 1985-1987, under the direction of Prof. K. S. Feldman.
- Ph.D. Medicinal Chemistry, The Ohio State University, 1985, under the direction of Prof. D. T. Witiak.
- B.S. Pharm., Magna cum laude, School of Pharmacy, University of Pittsburgh, April 1981.

Professional Service:

American Chemical Society, Organic and Medicinal Chemistry Divisions
Fellow, Royal Society of Chemistry
American Chemical Society Fellow

Division of Medicinal Chemistry, American Chemical Society:

- Treasurer 2015-present
- Five year term as Vice Chair/Long Range Planning Committee chair, Program Chair, Chair and past Chair (2004-2008). These roles required leadership and collaborative interactions nationally and internationally.
- Three year term as academic councilor (2012-2014)
- Member of program committee for 2014 National Medicinal Chemistry Symposium

Gordon Research Conference on Medicinal Chemistry

- 2012 vice chair elect
- 2013 vice chair
- 2014 chair

Co-editor, 3rd edition, Comprehensive Medicinal Chemistry 2017

Co-editor, 7th edition, Burger's Medicinal Chemistry 2007

Senior Editor, Royal Society of Chemistry series on Drug Discovery, 2008-present

Co-editor, "Successful Drug Discovery", (2014), Wiley VCH

Co-editor, "Analogue-Based Drug Discovery", volume 3, (2012), Wiley VCH

Program co-chair, National Medicinal Chemistry Symposium (2010)

Scientific Advisory Board National Medicinal Chemistry Symposium (2014)

Scientific Advisory Board Frontiers in Medicinal Chemistry 2014-2015

Organizer and conference co-chair for "Frontiers in CNS and Oncology Medicinal Chemistry", Siena, Italy, October 7-9, 2007, jointly organized with European Federation for Medicinal Chemistry.

Current Research Funding:

- RO1-AI133633-01, Development of inhibitors of *P. falciparum* cGMP dependent protein kinase (PfPKG) for malaria chemoprevention, 8/1/17-7/31/20, \$1.5MM direct costs, co-PI.
- Research Support, 9/1/11-8/31/16, ~\$60,000 annually, Margaret and Herman Sokol Endowment

Past Research Funding:

- Optimization of Novel Botulinum Toxin Protease A Inhibitors, 8/19/14-12/31/15, \$550,000 direct costs, Defense Threat Reduction Agency
- Protein Kinase Inhibitors for Parasitic Diseases, 4/1/15-12/31/15, \$89,000, Celgene Corporation
- Protein Kinase Inhibitors for Parasitic Diseases, 4/1/14-3/31/15, \$89,000, Celgene Corporation
- Protein Kinase Inhibitors for Parasitic Diseases, 4/1/13-3/31/14, \$115,000, Celgene Corporation
- Protein Kinase Inhibitors for Parasitic Diseases, 3/1/12-2/28/13, \$89,901, Celgene Corporation
- Purchase of LCMS, 10/1/13, \$70,000, Shimadzu Corporation
- Purchase of Essential Research Equipment, 10/1/12-9/30/14, \$100,000, co-PI with Dr. Vladimir Snitsarev, Montclair State University, Sokol Faculty Award Fund
- Lactam Inhibitors of Phospholipase A2, 7/1/88-6/30/90, direct costs \$25,000, Mississippi Affiliate, American Heart Association
- Novel Calmodulin Inhibitors, 7/1/89-6/30/91, direct costs \$35,000, Elsa U Pardee Foundation
- Phospholipase A2 Inhibitors as Novel Anti-inflammatory Agents, 7/1/89-6/30/91, direct costs \$200,000, American Lung Association

Publications:

1. "Stereocontrolled Syntheses for the Six Diasteromeric 1,2-Dihydroxy-4,5-Diaminocyclohexanes: Pt(II) Complexes and P388 Antitumor Properties", Donald T. Witiak, David P. Rotella, Joyce A. Filippi, and Judith Galucci, *J. Med. Chem.* **30**, 1327 (1987).
2. "Synthesis and P-388 Antitumor Properties of the Four Diastereomeric Dichloro 1-Hydroxy-3,4-diaminocyclohexane Pt(II) Complexes", Donald T. Witiak, David P. Rotella, Yong Wei, Joyce A. Filippi and Judith C. Gallucci *J. Med. Chem.* **32**, 214 (1989).
3. "Mechanistic and Preparative Studies of the Intramolecular Photocyclization of Methylated 2-(4-Pentenyl)tropones", Ken S. Feldman, Jon H. Come, Benedict J. Kosmider, Pamela M. Smith, David P. Rotella and Ming-Jung Wu, *J. Org. Chem.* **54**, 592 (1989).

4. "Homoallylically Controlled Epoxidation of Δ^4 -*cis*-1,2-Disubstituted Cyclohexenes", David P. Rotella, *Tetrahedron Letters*, 1913 (1989).
5. "Application of an Intramolecular Tropone-Alkene Photocyclization to the Total Synthesis of (\pm) Dactylol", Ken S. Feldman, Ming-Jung Wu and David P. Rotella, *J. Am. Chem. Soc.* **111**, 6457 (1989).
6. "Chloroperoxidase Mediated Halogenation of Phenols", Cheryl F. Wannstedt, David P. Rotella and Jerome F. Siuda, *Bull. Contamin. Environ. Toxicol.* **44**, 282 (1990).
7. "Stereocontrolled Iodolactonization of *Erythro* and *Threo* Tertiary Amides", David P. Rotella and Xun Li, *Heterocycles* **31**, 1205 (1990).
8. "The Total Synthesis of (\pm) Dactylol and Related Studies", Ken S. Feldman, Ming-Jung Wu and David P. Rotella, *J. Am. Chem. Soc.* **112**, 8490 (1990).
9. "Synthesis and Structural Analysis of Stereospecific 3,4,5-Trisubstituted γ -Butyrolactone Phospholipids", Xun Li and David P. Rotella, *Lipids* **29**, 211-224 (1994).
10. "The Effect of Pyrrolo[3,4-c]Carbazole Derivatives on Spinal Cord ChAT Activity" David P. Rotella, Marcie A. Glicksman, J. Eric Prantner, Nicola Neff and Robert L Hudkins, *Bioorganic and Medicinal Chemistry Letters*. **5**, 1167-1170 (1995).
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EXHIBIT 14

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

TORRENT PHARMACEUTICALS LIMITED and TORRENT PHARMA INC.,

Defendants/Counterclaim-
Plaintiffs.

Civil Action No. 17-3186-SRC-CLW

(CONSOLIDATED)

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED,

Plaintiffs/Counterclaim-
Defendants,

v.

INDOCO REMEDIES LTD.,

Defendant/Counterclaim-
Plaintiff.

Civil Action No. 17-7301-SRC-CLW

**REPLY EXPERT REPORT OF DAVID P. ROTELLA, PH.D.
REGARDING THE INVALIDITY OF U.S. PATENT NO. 7,807,689**

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I. INTRODUCTION

1. I submit this Reply Expert Report on behalf of Defendants Torrent Pharmaceuticals Limited and Torrent Pharma Inc. (collectively “Torrent”) and also on behalf of Indoco Remedies Ltd. (“Indoco”) in accordance with the Scheduling Order entered in the above-captioned matter.

2. I previously submitted an opening expert report in this case on June 14, 2019, titled “Opening Expert Report of David P. Rotella, Ph.D. Regarding the Invalidity of U.S. Patent No. 7,807,689” (the “Rotella Opening Report”), in which I included a description of my qualifications, education, professional experience, prior testimony, and compensation. (Rotella Opening Report, ¶¶ 2, 5-13).

3. Neither the nature of my opinions nor the outcome in this matter affects the amount of my compensation. I have no other financial interests in any of the parties to this dispute.

4. This Report sets out my opinions in reply to certain opinions expressed in the “Rebuttal Expert Report of Dr. David E. Nichols, Ph.D. on Validity of U.S. Patent Nos. 7,807,689, 8,288,539, and 8,173,663” (the “Nichols Rebuttal Report”) submitted by Plaintiffs Takeda Pharmaceutical Co. Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Ltd. (collectively, “Takeda”) on July 19, 2019, as well as the underlying bases for those opinions.

5. In forming my opinions, I considered and relied on my education, background, experience, training, and skills that I have accumulated over the course of my career. In addition, I have reviewed the Nichols Rebuttal Report and the documents cited therein to the extent they are related to Dr. Nichols’s opinions regarding the validity of U.S. Patent No.

7,807,689 (“the ’689 patent”), particularly to the extent they are related to the obviousness-type double patenting analysis for the ’689 patent, the documents identified in the Rotella Opening Report, and an updated list of materials that I have considered attached as Exhibit A of this Report.

II. SUMMARY OF OPINIONS

6. Dr. Nichols’s opinion that the asserted claims of the ’689 patent are not invalid for obviousness-type double patenting is incorrect. After reviewing Dr. Nichols’s Rebuttal Expert Report, I still hold all my opinions expressed in my opening report.

7. In particular, it is still my opinion that it would have been obvious to a POSA to modify the claimed compound in claim 162 of the Feng patent to arrive with a reasonable expectation of success (without the benefit of any hindsight) at the compound known as alogliptin that is claimed in the asserted claims of the ’689 patent.

8. It is still my opinion that claims 1, 3, 4, 9, 11-12, 43, and 49 of the ’689 patent are not patentably distinct from claim 162 of the Feng patent in view of Kim 1998 and in view of the common knowledge in the art.

III. PERSON OF ORDINARY SKILL IN THE ART

9. Dr. Nichols does not dispute the definition of the personal of ordinary skill in the art (“POSA”) with respect to the subject matter of the ’689 patent that I set forth in my opening report. (Nichols Rebuttal Report at ¶ 44; Rotella Opening Report at ¶ 65).

10. Instead, Dr. Nichols attempts to assert that I applied and relied upon a person with higher skills and more knowledge than a POSA. (Nichols Rebuttal Report, ¶ 44). I disagree. In my opinion, Dr. Nichols’s opinion that “a POSA would not be able to extract key structure-based

information from peptidic-like substrate/inhibitor DPP-IV enzyme crystal structures, extrapolate the recognition and interactions identified between the DPP-IV enzyme active site and the peptidic-like substrate/inhibitor, and then apply that information to the designing of non-peptidic DPP-IV inhibitors” is incorrect. (*Id.*)

11. Dr. Nichols is wrong in several aspects. *First of all*, without any support, Dr. Nichols simply assumed that a POSA would *have to* have the crystal structure information of a complex structure of DPP-IV and a non-peptidic inhibitor to design potential non-peptidic inhibitors. This is misleading. While I agree that the specific binding interactions and some binding properties with DPP-IV enzyme may differ between *certain* peptidic-like inhibitors and *certain* non-peptidic inhibitors, a POSA would have assumed and understood that the overall **key** interactions and binding properties with DPP-IV enzyme (for example, key interactions with S1, S2 binding pockets) are similar and can be used to ***design, identify, and/or evaluate*** potential non-peptidic inhibitors.

12. Most importantly, this was the general assumption in the art prior to 2004. *See* Lambeir A.M., et al., “*Dipeptidyl-Peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV*,” Crit. Rev. Clin. Lab. Sci. 40: 209–294 (2003) (“Lambeir”) at Plates 1 & 2 (showing the same interaction regions and active site for “substrates, inhibitors” in a schematic representation of the DPP-IV dimers *without differing* peptide-like inhibitors from non-peptidic inhibitors, even though the article discusses both types of inhibitors).

13. Dr. Nichols did not point to a single prior art reference that discloses or suggests that the interaction regions and binding properties are ***so different*** between peptide-like DPP-IV inhibitors and non-peptidic inhibitors that a POSA would not be able to use any of the crystal

structure information from a complex of a peptide-like inhibitor and DPP-IV to predict or otherwise form a reasonable expectation as to any binding information for a non-peptidic inhibitor. In fact, I am not aware of any prior art reference that suggests that the binding sites on DPP-IV are entirely different between peptide-like DPP-IV inhibitors and non-peptidic inhibitors.

14. Contrary to what Dr. Nichols asserts, the prior art suggests that a POSA would have used DPP-IV and its substrate/inhibitor complex's crystal structure information to design DPP-IV inhibitors *in general*, i.e., both peptide and non-peptide inhibitors. *See* Wiedeman at 418 ("With this information [of the first crystal structure with a bound inhibitor], advances in inhibitor design are expected."); *see also* WO 2004/011640 to Hiramatsu H. et al., titled "Three-Dimensional Structure of Dipeptidyl Peptidase IV," published on February 5, 2004 ("Hiramatsu"), at 3-4 (disclosing relying on crystal structures of human DPP-IV in free form to design DPP-IV inhibitors in general).

15. This is because the binding recognitions and interaction properties of a DPP-IV inhibitor depend on the specific mode of inhibition—whether it is competitive, noncompetitive, or mixed-type inhibition; not whether the inhibitor is a peptide-like inhibitor or a non-peptide inhibitor. A *competitive* inhibitor, by its definition, competes with a DPP-IV peptide substrate in binding to the same catalytic region. It was known in the art that non-peptidic inhibitors can also be competitive inhibitors (*see* Lambier at Table 2 (listing some non-peptidic inhibitors as competitive inhibitor), thus they are expected to bind to the same region of the DPP-IV as peptide substrate/inhibitors and have some degree of similar binding interactions with DPP-IV. In fact, in the field of DPP-IV inhibitors, competitive inhibitors are generally favored over non-competitive inhibitors for purpose of drug development because competitive inhibitors had been

best characterized in the art in terms of their structure-activity relationships and their biological effects in diabetes.

16. In other words, a POSA would have understood that non-peptidic small molecule inhibitors can also bind to the same site on DPP-IV as the substrate/peptide inhibitors; and have similar binding properties and interactions with DPP-IV, i.e., competitive non-peptidic inhibitors. Therefore, prior to March 2004, it would have been routine and obvious for a POSA to rely on the teaching about the general interactions and binding properties from crystal structure information from DPP-IV and the substrate/inhibitor DPP-IV complexes to design, search and identify with a reasonable expectation of success potential non-peptidic DPP-IV inhibitors.

17. Dr. Nichols is also incorrect to assume that the binding interactions of peptide-like substrate/inhibitors with DPP-IV are entirely different from those of non-peptidic inhibitors with DPP-IV, and that a POSA would not be able to use such information to design new non-peptidic inhibitors. In fact, recent comparative studies on the crystal structure data have confirmed what would have been generally understood by the POSA at the time of the alleged invention, that the several non-peptidic inhibitors, including alogliptin, sitagliptin etc., competitively bind *in the same sites* as the peptide substrate/inhibitor (tNPY) which was disclosed in Aertgeerts. (*See, e.g.*, Berger JP, et al., *A comparative study of the binding properties, dipeptidyl peptidase-4 (DPP-4) inhibitory activity and glucose-lowering efficacy of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin in mice*, Endocrinol. Diabetes. Metab. (2018) (“Berger”) at 1 (“The **common binding site** utilized by different DPP-4 inhibitors enables **similar competitive inhibition** of the cleavage of the endogenous DPP-4 substrates.”)(emphasis added); 4 (“While there are some differences between

the inhibitors in terms of binding potency. . . , they *all bind essentially in the same catalytic site*, thus behaving as *substrate competitive inhibitors*. All six inhibitors have small hydrophobic moieties that occupy the S1 pocket and hydrophilic groups that engage the primary residues involved in substrate recognition and binding, namely the side chains of Glu205, Glu206 and Arg125.”) (emphasis added).

18. For at least the foregoing reasons, I have applied the appropriate POSA as defined in Section VIII.B. of my opening report; and have *not* applied *nor* relied on a person having higher skills or more knowledge than the defined POSA in my opinion.

IV. DR. NICHOLS'S OPINION THAT THE ASSERTED CLAIMS OF THE '689 PATENT ARE NOT INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING IS INCORRECT

19. As an initial matter, I note that Dr. Nichols improperly and misleadingly ignores what in practice to the POSA is a simple, obvious “two-step” modification from the compound claimed in claim 162 of the Feng patent and alogliptin, and improperly characterizes the differences between the compound claimed in claim 162 of the Feng patent and alogliptin are “significant,” so that he could argue this “involve[s] such extensive modifications.” (Nichols Rebuttal Report, ¶¶ 270-272). In my opinion, as explained in my opening report and further below, because the goal of the POSA is to develop a novel, highly specific and potent, DPP-IV inhibitor class drug for the treatment of Type 2 diabetes, replacing the pyrimidinone scaffold in the compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil), either through the “scaffold replacement” or the “fluoro-olefin theory,” would be a natural and obvious (if not a fairly routine design) decision for a POSA in view of the prior art in total.

20. As part of the bases for his opinion, Dr. Nichols also asserts in part VII.A. of his rebuttal report that the properties of new chemicals were unpredictable, and that it would be

“**impossible** to predict” the resulting effect in terms of chemical properties or efficacy of a compound would have by replacing the scaffold with another scaffold, or even “**minor changes**” to a compound. (Nichols Rebuttal Report, ¶¶ 58-59). I disagree.

21. Dr. Nichols conveniently and completely overstates the level of unpredictability in the field of medicinal chemistry of DPP-IV and its inhibitors, as well as the requirement for an understanding of the *specific* structure-activity relationships for certain *specific* compounds. As I explained in my opening report, scaffold replacement approach based on available crystal structure of a target protein and cocrystal structures the protein and its substrate/inhibitors, including replacing the original scaffold with a fragment found from, e.g., searching an appropriate predefined database of fragments that would then return matching 3-D structures, or using molecules that were known in the art to have DPP-IV inhibition activity or anti-diabetic activity (for example, the uracil compound disclosed in Kim 1998), was commonly used by medicinal chemists to discover and design novel drug compound and has had many successful examples. (Rotella Opening Report, ¶¶ 19-21).

22. This is particularly the case in designing DPP-IV inhibitors. Prior to March 2004, the crystal structures of human DPP-IV both in free form and in complex with *several* small molecule inhibitors/substrates were reported and known in the art. (*See* Aertgeerts at 413). The general key binding interactions and binding properties of DPP-IV to its substrates/inhibitors, along with many discovered peptide-like and non-peptidic small molecule inhibitors, were already known in the art. (Rotella Opening Report, ¶¶ 19-35). Computer-aided designing and evaluating the binding properties of the resulting new compound with the new scaffold based on known crystal structure information of DPP-IV in both free and cocrystal form had been routine for the POSA. Thus, based on the computer-aided modeling, the POSA would have had a

reasonable expectation of whether a new compound would be a suitable DPP-IV inhibitor.

23. In fact, one of the inventors of the '689 patent reported in his own publication, Zhang, Zhiyuan et al., "*Design and Synthesis of Pyrimidinone and Pyrimidinedione Inhibitors of Dipeptidyl Peptidase IV*", 54 J. Med. Chem. 510-524 (2011) ("Zhang 2011"), which was cited and relied on by Dr. Nichols in his rebuttal report multiple times, that the discovery of aloglitpin started with design of new DPP-IV inhibitor based on the binding interactions and properties learned from cocrystal structures of DPP-IV and its substrate/inhibitors. (Zhang 2011 at 511). Zhang 2011 also reports that *based on such crystal structure information*, the inventor *successfully predicted* that a cyanobenzyl group can effectively fill into the S1 pocket and that the aminopiperidine motif can form the important salt bridge with E205/E206. As explained in my opening report, this aligns *exactly* with what was known in the art regarding the several key binding interactions at the time invention. (Rotella Opening Report, ¶¶ 25-26). Thus, at the very least, Zhang 2011 proves that Dr. Nichols is incorrect in asserting that the properties of new chemicals were unpredictable and that it would be "*impossible* to predict" the resulting effect in terms of chemical properties or efficacy of a compound.

24. Moreover, it is my understanding that the legal requirement for the obviousness-type double patenting does not require absolutely certainty. Rather, the relevant inquiry is what a POSA would have reasonably expected, not what a POSA would predict with certainty. I also understand that obviousness-type double patenting cannot be avoided simply by a showing of some degree of unpredictability in the art, so long as there was a reasonable probability of success. While there is no absolute certainty when it comes to medicinal chemistry, a POSA would have pursued paths in medicinal chemistry when there is just a reasonable expectation of success.

25. In addition, the inventor reported that alogliptin was discovered by examining the “replacement of the pyrimidinone ring [in a known xanthine inhibitor] with a pyrimidinedione ring” in a routine search for “more favorable” binding properties with DPP-IV. (*Id.*) Again, at the very least, Zhang 2011 itself confirms that scaffold replacement was a common practice at the time of the invention, and that Dr. Nichols is incorrect to assert that “. . . Dr. Rotella’s strategy of changing not just a single atom but an entire scaffold **would be highly unusual . . .**” (Nichols Rebuttal Report, ¶ 55).

26. Dr. Nichols also contends that the POSA would have needed the cocrystal structure of a xanthine-based DPP-IV inhibitor to develop a non-peptidic DPP-IV inhibitors. I disagree. As explained above (*supra* ¶¶ 11-18), the POSA would have been able to extract key binding interactions and properties based on cocrystal structure information from peptidic-like DPP-IV substrate/inhibitor DPP-IV enzyme crystal structures. The POSA would have been able to use the co-crystal structures of DPP-IV and inhibitors that bind to the active site of the DPP-IV to create a model to evaluate and assess how a structurally distinct inhibitor might bind to the active site of DPP-IV with a **reasonable** expectation of success (and no need for absolute certainty), because many competitive non-peptidic DPP-IV inhibitors were expected to have the same binding site and similar binding properties as the peptide-like substrate/inhibitors, as confirmed by Zhang 2011.

27. The POSA would then use the model to evaluate (and further modify) the potential DPP-IV inhibitor candidates (for example the Uracil analogues (1), (3) and (4) as described in the opening report) for their potential to interact favorably with DPP-IV, for example, the potential to interact favorably with S1 and S2 pockets of DPP-IV. It would have been routine experimentation for a POSA to evaluate the resulting enzyme-molecule complex

and choose the compound(s) with the most favorable features and potential to optimize.

A. Replacing the Pyrimidinone Scaffold in the Compound of Claim 162 of the Feng Patent with A Pyrimidinedione Scaffold (Uracil) Would Have Been A Natural and Obvious Choice for the POSA In View of Kim 1998

28. As explained in my opening report, prior to March 2004, it was a well-accepted and useful practice in drug discovery field to use scaffold replacement approach to develop novel compounds, and many researchers have successfully developed new molecules through this method. (Rotella Opening Report at ¶¶ 19-21.) A POSA would have particularly been motivated to use the scaffold replacement approach when the development goal was to design a novel, nonpeptidic small molecule inhibitor rather than a peptide-like inhibitor, which was exactly the situation that the POSA faced at that time. (*See Bohm* at 218 (“One of the most sought scaffold-variations is of course the move from peptidic ligands to “small molecules.”)).

29. Dr. Nichols incorrectly asserts that “a POSA would not have a reasonable expectation of success in pursuing a scaffold replacement/hopping theory, because there was no crystal structure information of the DPP-IV enzyme bound with a nonpeptidic inhibitor.” (Nichols Rebuttal Report, ¶ 284). Dr. Nichols’s assertion is based on a wrong premise that the structure information of the DPP-IV peptide inhibitor complex is entirely different from that of the DPP-IV non-peptidic inhibitor. As explained above in Section III *supra*, Dr. Nichols’s premise is incorrect, and so is his conclusion. As further explained below, his opinion does not rebut my opinion.

30. Dr. Nichols contends that a POSA would not consider Kim 1998’s uracil in developing a DPP-IV inhibitor to treat Type 2 diabetes because Kim 1998 does not mention DPP-IV, nor discloses whether uracil’s anti-diabetic activity is specific for Type 2 diabetes, and

because “nothing in Kim 1998 suggests that uracil would have particularly promising among the five compounds.” (Nichols Rebuttal Report, ¶¶ 286-289). I disagree.

31. First of all, the streptozotocin (STZ)-induced diabetic rat models used in Kim 1998 were well known in the prior art as Type 2 diabetes animal models. It was known in the art that streptozotocin was used to create animal models of non-insulin dependent diabetes, i.e., Type 2 diabetes. Thus, while Kim 1998 does not mention DPP-IV nor relate uracil’s anti-diabetic activity specific for Type 2 diabetes, the POSA would have readily recognized that the anti-diabetic activity of uracil in such an assay relates to Type 2 diabetes and merits further investigation, especially in view of the ability to lower blood glucose to a similar extent as a known drug Daonil® (glibenclamide) that is used to treat Type 2 diabetes. (Rotella Opening Report at ¶ 38, Table 1).

32. Further, as explained in my opening report, while Kim 1998 does not mention DPP-IV, the POSA, who is seeking to develop a new DPP-IV inhibitor drug for treatment of diabetes via computer-aided scaffold replacement and fragment-based screening from the database built on all DPP-IV inhibitors and small molecules that were known to bind DPP-IV, would have readily recognized the uracil ring as a part of the purine scaffold of the DPP-IV inhibitors disclosed in Wiedeman, Kanstrup 2003 and Mark 2004. (Rotella Opening Report at ¶¶ 37-39). Moreover, it was common knowledge in the art that DPP-IV inhibitors can be used for treatment of Type 2 diabetes. The POSA would thus readily and reasonably expect that inclusion of the uracil scaffold with other key structural features, such as the 2-cyanobenzyl and 3-aminopiperidinyl groups as described by Kanstrup 2003 and Mark 2004, was likely to result in an active DPP-IV inhibitor. (Rotella Opening Report at ¶¶ 31-35, 72).

33. Furthermore, while Kim 1998 reported anti-diabetic effect of five compounds, the commercially available anti-diabetic medication Daonil® was included as a positive control to compare the anti-diabetic effect of the other four compounds. The POSA would readily rule out Betaine because it has the lowest blood glucose inhibition effect. Among the three remaining tested components of the food preparation—uracil, rutin and ascorbic acid—a POSA would have readily understood the structures of the other two compounds (rutin and ascorbic acid), which have many **hydroxyl group (-OH)** and are thus very polar, would make them much less unlikely to bind to DPP-IV. (Rotella Opening Report, ¶38). This is because it was known in the art based on the known cocrystal structure of DPP-IV and its substrates/inhibitors that binding to DPP-IV requires binding with multiple primarily **hydrophobic** binding sites on DPP-IV. Thus, the POSA would have only considered uracil as a potential DPP-IV inhibitor.

34. Dr. Nichols argues that my illustration in Paragraph 79 of my opening report “does not account for the orientation of the respective proposed central rings in the context of the asserted retention of the 2-cyanobenzyl and 3-aminopiperidinyl groups.” (Nichols Rebuttal Report, ¶ 292). Dr. Nichols also attempts to improperly break down a **one-step** scaffold replacement into changes on an atom-to-atom basis. (Nichols Rebuttal Report, ¶¶ 293-296). I disagree. In my opinion, because the goal of the POSA is to develop a novel, highly specific and potent DPP-IV inhibitor for the treatment of Type 2 diabetes, replacing the pyrimidinone scaffold in the compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil), either through the “scaffold replacement” or the “fluoro-olefin theory,” would be a natural and obvious decision for a POSA in view of the prior art *in total*. The POSA would have a reasonable expectation of success based on the **overall** teaching of prior art, rather than atom-based piecemeal analysis in the core structure.

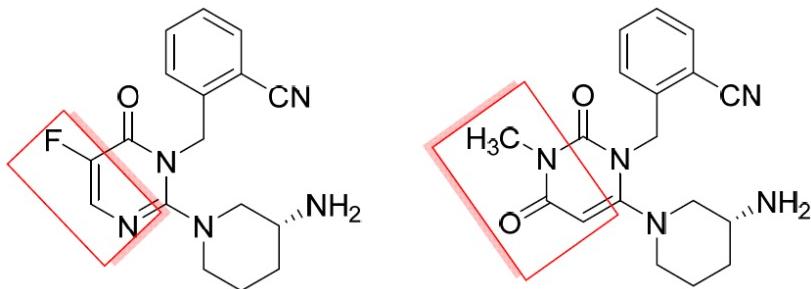
35. Dr. Nichols expresses a view of chemical structures in a simplified atom by atom comparison, rather than as a complete molecular entity as a POSA would have done. Dr. Nichols also appears to mischaracterize what a scaffold is. A scaffold is the *core* structure of a compound, and thus, by definition, exclude the attached groups on the core structure. Thus, the comparison of the two scaffolds in my opening report is a proper and accurate illustration of the two scaffolds.

36. In addition, the relative orientations of the 2-cyanobenzyl and 3-aminopiperidinyl groups on the central rings were taken into account during the scaffold replacement, which accordingly arrives at four different compounds (1-4) as illustrated in my opening report. (Rotella Opening Report, ¶ 81). The scaffold replacement approach replaces the scaffold at one step, and focuses on the overall improvement of binding interactions in a three-dimensional sense, rather than each specific atom's interaction change. As explained in my opening report, the POSA, who is aware of all of the relevant prior art at the time, based on all available information at the time, would have expected the uracil scaffold would appropriately occupy the hydrophobic core of the S2 pocket of DPP-IV based on the teaching of available crystal structure information of DPP-IV in both free form and bound form with substrates/inhibitors.

37. I also maintain my opinion regarding the side-by-side comparison of the formula of the pyrimidinone-based compound recited in claim and *R*-alogliptin as below. In my opinion, the orientation of the 2-cyanobenzyl and 3-aminopiperidinyl groups attached to the N atoms on the ring structures are properly aligned between the two structures.

**Claim 162
Compound**

***R*-alogliptin**



38. Dr. Nichols also contends that introducing a polar and hydrophilic oxygen substituent would not improve the binding in the hydrophobic S2 pocket. (Nichols Rebuttal Report, ¶¶ 295-298). I disagree. As the prior art expressly discloses that the S2 hydrophobic pocket is composed of the side chains of Arg 125, Phe 357, Tyr 547, Pro 550, Tyr 631, and Tyr 666, the POSA would have understood that, although the S2 pocket is considered to be hydrophobic, three out of the six amino acids are Tyrosine, which was known to have a polar hydroxyl group ($-\text{OH}$) on the nonpolar aromatic ring. The POSA would readily recognize that introducing a *similar* polar carbonyl group in an overall hydrophobic ring could improve the uracil ring alignment with one of the Tyrosine side chain ($-\text{OH}$ group). In fact, because of introduction of the polar carbonyl group on the uracil ring, the POSA would have particularly been motivated to introduce a hydrophobic group (methyl group) at the N3-hydrogen position to balance the overall polarity of the core structure (i.e., to offset the hydrophilicity introduced by the carbonyl group). (Rotella Opening Report, ¶ 85).

39. Dr. Nichols also seems to focus on the change of certain *local* interactions when evaluating new inhibitors for interactions with the active site of DPP-IV. For example, Dr. Nichols points out (without evidence) that the fluorine in the compound of claim 162 is capable of forming hydrogen bond while the methyl group at the same position in alogliptin cannot form hydrogen bond; and that the oxygen on the carbonyl group of uracil-based compounds can form

hydrogen bond while the hydrogen at the same position in compound of claim 162 cannot form hydrogen bond. (Nichols Rebuttal Report, ¶¶ 296-297). Dr. Nichols's analysis overlooks the possibility that new hydrogen-bonding interactions formed with the uracil-based compounds, which can be identified with the help of the computer-based modeling, can offset the lost hydrogen bonding identified by Dr. Nichols.

40. In my opinion, a POSA would not have seen any impediment from such local interactions. The POSA would have understood that binding interactions between molecules are not rigid, but dynamic and that a new scaffold can provide interactions to replace those in the original. As explained above, with computer-aided modeling, the POSA would have recognized that the *overall* binding interactions with DPP-IV are promising in the new compound alogliptin— favorable hydrophobic interactions along with uracil ring stacking interactions with Tyrosine. In addition, based on computer modeling information, a POSA would have expected that the introduction of the carbonyl group which acts as a hydrogen bond acceptor is situated to form a hydrogen bond with either the backbone NH group of the amino acid in the S2 pocket or the -OH group of one of the Tyrosine residues in the S2 pocket of DPP-IV. Such hydrogen bond can offset losing the hydrogen bond formed by fluorine in compound of claim 162, if such a hydrogen bond formed at all.

41. Dr. Nichols also contends that the Feng patent did not report the specific potency or any selectivity data of the compound in claim 162, but merely a range of the inhibition potencies, and that a POSA would have no reason to optimize only the pyrimidinone core. (Nichols Rebuttal Report, ¶ 303). I disagree.

42. Dr. Nichols seems to confuse an obviousness-type double patenting analysis with a regular obviousness analysis. It is my understanding that there is no selection of lead

compound step in an obviousness-type double patenting analysis because the issue is double patenting, and thus the issue is not whether a POSA would have selected the compound in claim 162 as a lead compound for modification; the issue instead is whether a POSA would have had reason or motivation to modify the compound in claim 162 to arrive with a reasonable expectation of success at a molecule that is alogliptin. For this reason, whether the Feng patent reports the specific potency or any selectivity data of the compound in claim 162 is irrelevant. Regardless, the POSA would have understood that this compound has a suitable inhibition potency and favorable selectivity properties on DPP-IV as it is the only exemplary compound that is separately claimed in the claims of the Feng patent. As explained in detail in my opening report, the POSA would have retained the 2-cyanobenzyl group and aminopiperidinyl groups on the pyrimidinone-based compound based on the disclosure in the prior art and focuses on the core structure to develop a novel, potent DPP-IV inhibitor. (Rotella Opening Report, ¶¶ 71-74).

43. Accordingly, for at least the above reasons, the POSA would have expected that the uracil core structure would be able to suitably occupy the S2 pocket of DPP-IV with suitable interactions with amino acid residues that create this pocket. Nothing in Dr. Nichols's opinion changes my opinion.

B. The POSA Would Have Also Been Motivated to Replace the Pyrimidinone Scaffold in the Compound of Claim 162 with A Pyrimidinedione Scaffold (Uracil) In View of the Common Knowledge About Fluoroolefin Moiety In DPP-IV Inhibitors

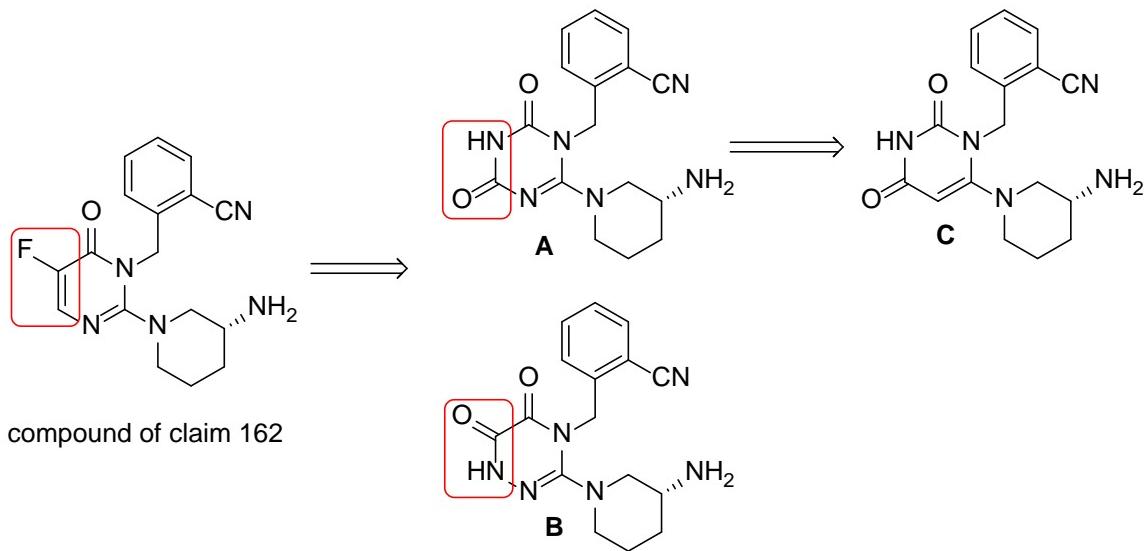
44. As explained in my opening report, the POSA would have also separately (but additionally) been motivated to directly replace the pyrimidinone scaffold in the compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil) based on the common knowledge in the art that a fluoro-olefin mimics an amide bond in DPP-IV inhibitors, i.e., a fluoro-olefin and amide bond are considered by a POSA as isosteres in DPP-IV inhibitors.

(Rotella Opening Report, ¶¶ 80, 84). This modification is essentially replacing the fluoro-olefin group in the core structure with an amide bond. For the convenience of discussion here, I also refer this as “the fluoroolefin replacement” hereinafter.

45. Dr. Nichols first contends that Torrent waived this argument because “Evans was not part of its contentions.” While I am not a legal expert, I’d like to correct one fact: the knowledge that fluoro-olefin mimics an amide bond in DPP-IV inhibitors was commonly known in the art. For example, Lambeir also discloses fluoro-olefin isosteres as DPP-IV inhibitors. (Lambeir at Table 2; *see also* Jian Lin & John Welch et al., “*Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics*,” Proc. Natl. Acad. Sci. USA, Vol. 95, pp. 14020-14024 (1998) (“Welch”) at 14020-21). In addition, the two fluoro-olefin derivative DPP-IV inhibitor examples disclosed in Evans were independent studies from **different** research groups. (*See* Evans at 578, 581). This suggests that a fluoro-olefin and an amide bond are considered by a POSA as isosteres and a replacement between the two was well known in the field of DPP-IV inhibitors. In other words, the POSA would have known this from common knowledge in the art, and would not have to specifically rely on Evans or any other reference to be motivated to make this fluoro-olefin replacement.

46. Dr. Nichols also contends that replacement of fluoro-olefin with an amide group requires that the fluorine substituent of the fluoro-olefin be aligned with the oxygen substituent of the amide which it is replacing. (Nichols Rebuttal Report at ¶ 317). Dr. Nichols relies on Figure 32 in Lee 1990 to support this allegation. I disagree. Nothing in Lee 1990 teaches or even suggests that one **must** align the fluorine with the oxygen of the amide group to make a replacement in a drug design. Since a fluoro-olefin and amide bond are considered by a POSA as isosteres, this means that one can be employed to replace the other in a potential DPP-IV

inhibitor. In my opinion, at a minimum, the POSA would have motivated to try the fluoro-olefin replacement in both ways and produce with a reasonable expectation of success two outcomes: one as shown in Dr. Nichols's illustration (shown as compound B below), and the other one results a new structure shown as compound A:



47. The POSA would have easily recognized that the resulting compound B contains a hydrazine like functional group, i.e., a nitrogen-nitrogen bond, which was known in the art as potential carcinogenic and toxic. (*See infra ¶¶ 49-50; Rotella Opening Report, ¶ 82*). As a result, even assuming that the POSA would have replaced the fluoro-olefin with an amide group with the oxygen aligned with fluorine as Dr. Nichols alleged, the POSA would then not have chosen compound B for further optimization and development.

48. As explained above (*supra ¶¶ 25-27*), the POSA would have been able to use the model created from the crystal structure information from DPP-IV and inhibitors that bind to the active site of the DPP-IV to evaluate how different inhibitors might bind to the active site of DPP-IV. The POSA would have used the model to evaluate and further optimize the resulting compound A for its potential to interact favorably with DPP-IV with a reasonable expectation of

success. In light of the teaching in Kim 1998, the POSA would have further recognized that compound A can result in a uracil-based compound C (shown above, i.e., Uracil analogue (1)) by replacing a single nitrogen with carbon to arrive at compound C. The scaffold in compound C is uracil and the aminopiperidine and cyanobenzyl moieties are appended to the scaffold. The POSA would have reasonably expected that this obvious change would provide favorable interaction with DPP-IV.

49. Accordingly, the POSA would not have made the fluoro-olefin replacement in the way as Dr. Nichols suggests (i.e., aligning the fluorine atom with the oxygen atom), because it would result a potential toxic compound. Rather, the POSA would have made the fluoro-olefin replacement without aligning the fluorine atom with the oxygen atom to arrive at the compound with the uracil ring.

C. The POSA Would Have Been Motivated to Replace the N3-hydrogen With A Hydrophobic Methyl Group In the Three Uracil Analogues and Arrived at Alogliptin with A Reasonable Expectation of Success

50. As explained in my opening report, the POSA would have arrived at four uracil analogues after replacing the pyrimidinone ring in the compound in claim 162 with a uracil ring in view of Kim 1998. (Rotella Opening Report, ¶ 81). The POSA would have selected uracil analogues (1), (3) and (4) for further optimization because uracil analogue (2) is a hydrazine derivative. (Rotella Opening Report, ¶ 82).

51. Dr. Nichols, however, contends that the POSA would not have found uracil analogue (2) undesirable for this reason. Specifically, Dr. Nichols relied on Sinha, Birandra et al., “Biotransformation of Hydrazine Derivatives in the Mechanism of Toxicity”, 5(2) J. Drug Metabolism & Toxicity 1-6 (2014) (“Sinha”) and alleged that there are many approved drugs contain a hydrazine. (Nichols Rebuttal Report, ¶ 312).

52. Dr. Nichols simply misses the point. Sinha expressly discloses that *all* those listed hydrazine derivative drugs, while being used to treat certain diseases, can induce “significant undesirable effects (or toxicity)”. For example, Hydralazine, a drug for management of high blood pressure, can induce the development of severe form of systemic lupus; Iproniazid, an antidepressant, has been withdrawn from clinical use due to its severe hepatotoxicity in humans, and so on. Thus, even though uracil analogue (2) may be developed as a viable DPP-IV inhibitor itself, for exactly the reasons (i.e., likely causing significant side effects and toxicity otherwise) set forth in Sinha, the POSA would have not selected uracil analogue (2) for further optimization.

53. Dr. Nichols’s also argues that the POSA would not prioritize uracil analogue (1) over uracil analogue (3) or (4), but even in the structures prepared by himself shows that Uracil analogue (1) has a closer analogy to the original pyrimidinone-based compound recited in claim 162 of the Feng patent. (Nichols Rebuttal Report, ¶ 313). Specifically, both 2-cyanobenzyl and 3-aminopiperidinyl group are still attached to the N atom on the ring of Uracil analogue (1) as those groups attached to the ring of claim 162 of the Feng patent.

54. I also find Dr. Nichols’s argument to be specious. Even assuming for the sake of argument that the POSA would not prioritize Uracil analogue (1), and optimize Uracil analogues (1), (3) and (4) at the same time, the POSA would have had a reasonable expectation of success of still arriving at the molecule alogliptin because selecting alogliptin from such a small number set of compounds would be a matter of routine experimentation.

55. As explained above (*supra* ¶ 38), the POSA would have been motivated to replace the N-3 hydrogen in the three Uracil analogues with a small hydrophobic group such as methyl group to offset the introduction of a polar carbonyl group in the core structure, in order to

optimize the binding interactions with DPP-IV.

56. Accordingly, I maintain my opinion that it would have been to a POSA a logical, routine and obvious modification to modify the compound recited in claim 162 of the Feng patent (in view of Kim 1998 and the common knowledge known in the art) to arrive with a reasonable expectation of success at the compound that is claimed in the '689 patent—alogliptin.

D. It Would Have Been Obvious for the POSA to Make the Benzoate Salt Form of Alogliptin

57. Dr. Nichols contends that “even were it obvious to start with alogliptin, which it is not, preparing and characterizing all the potential salts would be a major undertaking.” (Nichols Rebuttal Report, ¶ 341). I disagree with Dr. Nichols.

58. Dr. Nichols argued that benzoate is “rarely [used] for salt formation,” and that “the FDA has approved many more salts” since the 53 anions that FDA has approved in 1997. (*Id.*). However, in Table 1 of Bighley & Berge 1996, the very reference that Dr. Nichols relied on, the percent of Benzoate salt among the total anionic salts in use is higher than ***more than 50*** of the other listed approved anionic salts. (See Bighley & Berge 1996 at 454-455, Table 1).

59. More importantly, as alogliptin is a DPP-IV inhibitor with both 2-cyanobenzyl and 3-aminopiperidinyl groups, the POSA would have started with the salts that have been used with DPP-IV inhibitors with similar side chains in searching a suitable salt for alogliptin. As mentioned in my opening report, Kanstrup 2003 reports non-peptidic xanthine-based DPP-IV inhibitors with both 2-cyanobenzyl and aminopiperidinyl groups, it would have been obvious for the POSA to try the salts disclosed in this prior art reference, which discloses the benzoate salt for the DPP-IV inhibitors. (Kanstrup 2003 at p. 18, ll.25-33). In addition, it was well-known that an active ingredient salt that forms a single polymorph (as opposed to a salt that provides

multiple polymorphic forms) is more likely to be approved by the FDA because a stable, single polymorph form provides consistent properties. Benzoate was well known in the art as a favored organic salt because it is considered safe and non-toxic.

60. For at least these reasons, it would have been not only obvious but routine for the POSA to use a benzoate salt of alogliptin. I maintain my opinion that claims 9, 11 and 12 of the '689 patent are not patentably distinct from claim 162 of the Feng patent.

E. Claim 162 of the Feng Patent Should Be Construed to Recite the (*R*)-Enantiomer

61. Dr. Nichols also argues that the POSA would have to “*choose* construing claim 162 to ‘correct’ the depicted compound from being a racemate into a single enantiomer, despite claim 162 illustrating the compound without any stereochemistry and not including any language indicating the claim is limited to a single stereoisomer of the compound.” (Nichols Rebuttal Report, ¶ 274).

62. Dr. Nichols seems to have either conveniently ignored the obvious clerical error in claim 162 of the Feng patent, or has applied and relied on a person having much lower level skills than the POSA. As I explained in detail in my opening report, claim 162 of the Feng patent depends on claim 161, but recites exactly the same chemical structure. (Rotella Opening Report, ¶¶ 53-54). This would have been an obvious error to a POSA. Most importantly, the prosecution history of the Feng patent confirms that this is a clerical error made during the prosecution. In addition, *nearly all* the 36 examples (except only a few examples that did not specify a stereoisomer of the compound) disclosed the specification of the Feng patent specify the (*R*)-enantiomer of the 3-aminopiperidinyl group, rather than the (*S*)-enantiomer. Thus, the POSA would readily understand that claim 162 should be construed as the compound with the

(*R*)-enantiomer for the 3-aminopiperidinyl group. (Rotella Opening Report, ¶¶ 50-54).

63. Dr. Nichols also contends that claim 3 of the '689 patent is patentably distinct from claim 162 because "claim 3 requires the claimed compound comprise a single enantiomer," and that "claim 162 of the '344 patent does not specify a stereoisomer of the compound depicted." (Nichols Rebuttal Report, ¶ 328). Dr. Nichols also made similar argument with respect to claim 11. (Nichols Rebuttal Report, ¶ 351). I disagree.

64. As explained above, claim 162 should be clearly construed to specify the (*R*)-enantiomer for the 3-aminopiperidinyl group. The fact that claim 3 or claim 11 "reads on either the compound illustrated below as the (*R*)-enantiomer configuration or the (*S*)-enantiomer configuration," does not add anything novel or non-obvious. Thus, it is still my opinion that claims 3 and 11 are not patentably distinct from claim 162 of the Feng patent.

V. THERE IS NO EVIDENCE OF UNEXPECTED RESULTS OR TEACHING-AWAY THAT IS PROBATIVE OF NON-OBVIOUSNESS

65. In the Rotella Opening Report, I set out my understanding of certain legal principles as they related to forming my opinions in that Report. (Rotella Opening Report at Section VIII.A).

66. In addition, I have also been informed and understand that when evaluating the objective indicia of unexpected results, the purported unexpected results should be evaluated based on what a POSA would or would not have expected at the time of the invention. I further understand that that in order to allege unexpected results, the results of the claimed invention must be compared to the results of the closest prior art. I also understand that for an alleged unexpected result to be probative of non-obviousness, there must be evidence showing a difference in kind, not just in degree, as compared to the closest prior art.

67. I have also been informed and it is my understanding that there must be a nexus between any alleged evidence of secondary considerations of nonobviousness and the claims of the '689 patent. Furthermore, any alleged secondary considerations must also be commensurate in scope with the claimed invention.

68. As discussed in my opening report, the POSA, who was seeking to develop a novel, highly specific and potent DPP-IV inhibitor and starting with the pyrimidinone-based compound (claim 162), would have been motivated to retain the 2-cyanobenzyl group on the pyrimidinone based compound because this structure element suitably occupies the S1 binding pocket of DPP-IV. (Rotella Opening Report, ¶ 72). This is because the binding interactions with the S1 binding site of the DPP-IV was known in the art determining the *binding specificity* of substrate/inhibitors. (Rotella Opening Report, ¶ 26). Furthermore, the POSA would have been motivated to replace the pyrimidinone scaffold in the compound of claim 162 of the Feng patent with a pyrimidinedione scaffold (Uracil), in part because there was a reasonable expectation that the resulting uracil scaffold would bind suitably in the hydrophobic S2 pocket of DPP-IV, which was known important for inhibitor recognition and binding. (Rotella Opening Report, ¶¶ 78-79). Therefore, the POSA would have a reasonable expectation that the resulting compound would have appropriate binding interactions with *both* S1 and S2 binding sites of DPP-IV, and thus significant potency and selectivity (determined by binding specificity) for DPP-IV. In other words, the POSA would have expected that the resulting compound would have significant inhibition potency and selectivity for DPP-IV.

69. Dr. Nichols cites Lankas, George R., et al., *Dipeptidyl Peptidase IV Inhibition for the Treatment of Type 2 Diabetes*, 54 DIABETES 2988 (2005) ("Lankas") as alleged evidence of the unexpected improved selectivity for DPP-IV over other DPP enzymes. However, Lankas

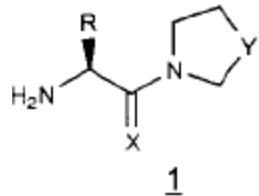
does not support that Dr. Nichols's allegation that “[t]he DPP-4 inhibitors that existed before alogliptin were not very selective for DPP-4 over other DPP enzymes.” (Nichols Rebuttal Report, ¶ 372(1)). At minimum, Lankas reports that sitagliptin, which existed before alogliptin (and known as “DPP-IV selective compound 3” in Lankas), has very good selectivity for DPP-IV over other DPP enzymes. (Lankas at 2992, Table 3). Furthermore, none of the DPP-8/9 selective or QPP selective inhibitors reported in Lankas are structurally similar to alogliptin or the compound in claim 162 of the Feng patent. Thus, Lankas in no way supports Dr. Nichols's assertion that alogliptin's high specificity for DPP-IV is unexpected.

70. Dr. Nichols also alleges that, because replacing a bicyclic ring in the xanthine rings with a monocyclic ring as in alogliptin would reduce the π - π interaction, a POSA “would expect that the decreased interaction between Alogliptin and DPP-4 would reduce the stability, thus rendering Alogliptin a less potent inhibitor,” and thus, according to Dr. Nichols, it is surprising[]” that “Alogliptin is a more potent DPP-IV inhibitor.” (Nichols Rebuttal Report, ¶ 372(2)). Dr. Nichols relies on Zhang 2011 to show that alogliptin has smaller π -bonding surface than xanthine compound. However, Zhang 2011 does not support Dr. Nichols's allegation that there is “decreased interaction between Alogliptin and DPP-4.” Quite on the contrary, Zhang 2011 expressly discloses that “the uracil ring [of alogliptin] π -stacks with Tyr-547,” without suggesting that such a π -stacking interaction is weaker than that observed in the xanthine ring. (Zhang 2011 at 514). While alogliptin has smaller π -bonding surface than xanthine compound, this does not necessarily mean that the π -stacking interaction with the uracil ring in alogliptin is weaker than that in the xanthine ring because the π -stacking interaction depends on both the angle between the ring planes and the distance between the ring centroids, but not the surface area of the ring. In addition, a POSA would recognize experimentally

measuring the strength of such interactions in an enzyme-inhibitor complex is challenging. Thus, the POSA would only note that such an interaction exists, and might contribute to binding to DPP-IV, but the strength of this interaction would not be quantified. Furthermore, Figure 9 of Zhang 2011 clearly shows that “cyanobenzyl group effectively fills the S1 pocket (formed by Val656, Tyr631, Tyr662, Trp659, Tyr666, and Val711) and interacts with Arg125.” (Zhang 2011 at 514). There is no such interaction formed with Arg125 in the cocrystal structure of DPP-IV and the xanthine compound. (*Compare* Zhang 2011 at Figs. 1&2 with Fig. 9). In other words, Zhang 2011 actually reports that there are *increased* interactions between alogliptin and DPP-IV and thus increased potency, as the POSA would have reasonably expected.

71. As explained above in Section IV.D. (*supra* ¶¶ 57-60), there is nothing unexpected with respect to the benzoate salt of alogliptin. At the time of the invention, benzoate salt has been used with other non-peptidic DPP-IV inhibitors, particularly as the salt form for the xanthine-based DPP-IV inhibitors with the same side chains as alogliptin.

72. Finally, there is no prior art that taught away from alogliptin. Dr. Nichols points to a statement in Villhauer that “[s]ubstituting the pyrrolidine ring with 6- or 7-membered rings or acyclic amines results in a loss of potency” as evidence of teaching away. (Nichols Rebuttal Report, ¶ 373). However, this statement was clearly made in the context of discussing certain specific “peptide-like inhibitors,” the “aminoacyl pyrrolidides and thiazolidides” which have the general structure shown as below. The POSA would not have considered this statement as relevant in seeking to develop a new nonpeptidic small molecule DPP-IV inhibitor. Accordingly, Dr. Nichols’s alleged evidence of teaching away is irrelevant and unavailing since it is based on an incorrect interpretation and application of the prior art reference.



73. For the foregoing reasons, it is my opinion that Dr. Nichols has not identified any evidence of objective indicia that would support the non-obviousness of the asserted claims of the '689 patent. I maintain my opinion, as laid out in my opening report, that claims 1, 3, 4, 9, 11-12, 43 and 49 of the '689 patent are invalid for obviousness-type double patenting over claim 162 of the Feng patent in View of Kim 1998 and common knowledge in the art.

VI. SUPPLEMENTATION AND REBUTTAL

74. This Report sets forth my professional opinions based only on information available as of the date that I have signed this Report below. In the event that additional data or testimony is made available, I may find it appropriate to revise or supplement my opinions. I also reserve the right to clarify, amend or supplement my opinions in response to any issues raised by Plaintiffs, evidence presented by them, or any additional information that I become aware of later or may be made available to me in the future, including documents or information produced in this litigation, or information disclosed at depositions or set forth in any reports submitted by Plaintiffs' experts.

75. I expect to be called to testify at trial in the above-captioned consolidated actions regarding the matters set forth in this Report. If called to testify at trial, I may explain principles and terminology referred to or related to issues in this Report, as well as any of the documents referenced in the Report. I reserve the right to convey my opinions through the use of demonstrative exhibits at trial. I have not yet created all of the exhibits I may use at trial, but if I choose to, such exhibits may be of varying scope in order to assist in explaining what is set forth

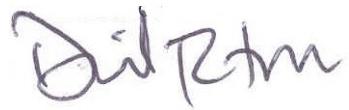
my reports and as needed to respond to any opinions raised by Plaintiffs' experts in their reports or during their depositions. I may also comment on or testify at trial in response to the testimony of other witnesses, including witnesses who testify on behalf of Plaintiffs at trial or during depositions.

76. I reserve the right to testify, expound on and/or express further opinions on issues or matters related to my opinions in this Report or later raised in this litigation, including as necessary (1) to rebut any matters testified to by Plaintiffs' experts or opinions including as expressed by Plaintiffs' experts in their expert reports; (2) during my deposition; and (3) at trial.

VII. CONCLUSION

77. For the reasons explained in this report, it is still my opinion that from the perspective of a POSA, claims 1, 3, 4, 9, 11-12, 43, and 49 of the '689 patent are not patentably distinct from claim 162 of the Feng patent in view of Kim 1998 and the common knowledge in the art, and therefore, are invalid for obviousness-type double patenting.

Signed this 23rd day of August, 2019.



DAVID P. ROTELLA, PH.D.

EXHIBIT A**Materials Considered**

Description	Document Production Range
U.S. Patent No. 7,807,689	TAK-ALOG 00413714 - TAK-ALOG 00413768
Portions of File History of U.S. Patent No. 7,807,689	TAK-ALOG_00156012 - TAK-ALOG_00186127
U.S. Patent No. 7,723,344 to Feng et al. "Dipeptidyl Peptidase Inhibitors" issued on May 25, 2010	TOR-NESINA 00127019-TOR-NESINA 00127088
Portions File History of U.S. Patent No. 7,723,344	TOR-NESINA 00142001-TOR-NESINA 00143216
Kanstrup <i>et al.</i> , WO 03/004496 entitled "DPP-IV-Inhibiting Purine Derivatives for the Treatment of Diabetes", published January 16, 2003	IndAlo0000738-IndAlo0000839
Evans, Michael D., "Dipeptidyl peptidase IV inhibitors" <i>II Drugs</i> 2002 5(6):577-585	IndAlo0000840-IndAlo0000848
Anderson, Amy C. "The Process of Structure-Based Drug Design" <i>Chemistry & Biology</i> , Vol. 10, 787-797, (September 2003)	IndAlo0000966-IndAlo0000976
McGaughey, Georgia B., et al., "π-Stacking Interactions," <i>The Journal of Biological Chemistry</i> , Vol. 273, No. 25, Issue of June 19, pp. 15458–15463 (1998)	TOR-NESINA 00126996-TOR-NESINA 00127002
Bohm et al., "Scaffold hopping," <i>Drug Discovery Today: Technologies</i> 2004, Vol. 1, No. 3, 217-223 (December 2004)	TOR-NESINA 00127789-TOR-NESINA 00127796
Aertgeerts, K., et al., "Crystal structure of human dipeptidyl peptidase IV in complex with a decapeptide reveals details on substrate specificity and tetrahedral intermediate formulation", 13(2) <i>PROTEIN SCI.</i> 412-421 (Feb. 2004)	TOR-NESINA 00126326-TOR-NESINA 00126335
Engel, M., et al., "The crystal structure of dipeptidyl peptidase IV (CD26) reveals its functional regulation and enzymatic mechanism", 100(9) <i>PNAS</i> 5063-5068 (Apr. 29, 2003)	IndAlo0000946-IndAlo0000951
Lambeir, A., "Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV", 40(3) <i>Crit. Rev. Clin. Lab. Sci.</i> 209-294 (2003)	IndAlo0000858-IndAlo0000945
Wiedeman, P.E. & Trevillyan, J.M., "Dipeptidyl peptidase IV inhibitors for the treatment of impaired glucose tolerance and type 2 diabetes", 4(4) <i>Current Opinion in Investigational Drugs</i> 412-420 (Apr. 2003)	IndAlo0000849-IndAlo0000857

C.A. Patent No. 2,496,249 to Mark et al., entitled “8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments,” published on March 4, 2004 (“Mark 2004”)	TOR-NESINA 00127532-TOR-NESINA 00127751
C.A. Patent No. 2,435,730 to Lotz et al., entitled “xanthines derivatives, the production thereof and their use as pharmaceutical compositions,” published on September 6, 2002 (“CA ’730”)	IndAlo0000374-IndAlo0000737
Kim et al., “Anti-diabetic Activity of Constituents of Lycii Fructus,” The Journal of Applied Pharmacology, Vol. 6, pp. 378-382 (1998) (“Kim 1998”)	TOR-NESINA 00126805-TOR-NESINA 00126810
S. Parodi, et al., “DNA-damaging Activity In Vivo and Bacterial Mutagenicity of Sixteen Hydrazine Derivatives as Related Quantitatively to their Carcinogenicity,” Cancer Research 41, 1469–1482, April 1981	TOR-NESINA 00126607-TOR-NESINA 00126621
Lal et al., “Electrophilic NF Fluorinating Agents,” Chemical Reviews, 1996, Vol. 96, No. 5, pp. 1737-1755	TOR-NESINA 00126976-TOR-NESINA 00126995
Berge et al., “Pharmaceutical Salts,” Journal of Pharmaceutical Sciences, Vol. 66, pp. 1-19 (1977)	TOR-NESINA 00127344-TOR-NESINA 00127364
Hiramatsu, H. et al., WO 2004/011640 A1 entitled “Three-Dimensional Structure of Dipeptidyl Peptidase IV”, published February 5, 2004	TOR-NESINA 00143230-TOR-NESINA 00143565
Lin, Jian & John Welch et al., “Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics” Proc. Natl. Acad. Sci. USA, Vol. 95, pp. 14020-14024 (1998)	TOR-NESINA 00143225-TOR-NESINA 00143229
Berger, Joel P. et al., “A comparative study of the binding properties, dipeptidyl peptidase-4 (DPP-4) inhibitory activity and glucose-lowering efficacy of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin in mice” Endocrinol Diab Metab. 2018; 1:e2. https://doi.org/10.1002/edm2.2	TOR-NESINA 00143217-TOR-NESINA 00143224